ALLERGY IN

PEDIATRIC PRACTICE

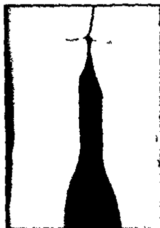






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PEDIATRIC PRACTICE

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PREFACE

A large proportion of the infants and children suffering from allergic diseases are necessarily treated by general practitioners and pediatricians without special training in allergy. This book is intended to offer such physicians practical aid in the diagnosis and treatment of these conditions.

It presents in detail the views and methods that we have found most useful in actual practice. Most of the material included is familiar to and accepted by the majority of specialists in the field. However, there are certain problems, both theoretical and practical, on which various authorities hold sharply divergent opinions. An attempt has been made to indicate the existence of these differences of opinion and to differentiate fact from theory, but the desire to keep the book simple and practical does not permit detailed and impartial presentation of all points of view on controversial problems.

In keeping with the intent of the book, many conditions which have been suspected of being allergic on scanty or inadequate evidence receive little or no mention. Attention is focused on those diseases in which allergic methods of diagnosis and treatment have proved of real practical value.

A certain amount of basic scientific background is included. It is believed that this knowledge is essential for intelligent use of the actual diagnostic and therapeutic methods. Since the book is intended for practitioners without special training in the field, it seems safe to assume that this information is either new to them or long since forgotten.

The citation of references to other publications is intended to indicate relatively few sources from which more detailed information and bibliographies may be obtained. In most cases these are review articles or books rather than original sources. References are intended to support specific statements in the text only when these are relatively unfamiliar or at variance with generally held opinions. No attempt is made to indicate the ultimate source of widely known facts.

We wish to express our indebtedness to Dr. Robert A. Cooke, under whom we both received training in this branch of medicine. His opinions and methods form so large a part of the material included in this book that detailed acknowledgment would be impractical.

Thanks are also due to the Institute of Allergy of The Roosevelt Hospital for most of the illustrations and to Miss Marcelle Johnson for aid in preparing the manuscript

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Chapter 1

INTRODUCTION

HISTORICAL BACKGROUND

Ancient and medieval medical writings contain references to individual idiosyncrasies to foods and odors which in the light of present knowledge are recognizable as examples of allergic disease Jenner in his account of vaccination for smallpox in 1798 described the accelerated reaction to the virus in persons who had previously been vaccinated an example of altered reactivity obviously related to previous contact with the causative agent More definite descriptions of allergic phenomena date from the nineteenth century Bostock in 1819 described hay fever from which he himself suffered under the name of summer catarrh In a subsequent publication in 1828 he stated that the condition was popularly known as hay fever because of the belief that it resulted from the effluvium of new hay However he did not himself accept this explanation but attributed the symptoms to exposure to the summer sun Blackley in 1873 clearly showed that the condition was produced by grass pollen and described the reactions noted when pollen was placed in a scratch in the skin or the conjunctival sac During the same period Salter and others also attributed asthma to idiosyncrasy to various extrinsic materials such as animal danders Further evidence of acquired idiosyncrasy to infective agents was furnished by Koch in his accounts of tuberculin sensitization of animals infected with tubercle bacilli late in the nineteenth century

While these observations furnished examples of unusual individual reactions to foreign materials correlation and explanation of the phenomena awaited the development of the concept of immunity to infections and toxins acquired through previous contact Portier and Richet in studying the immunization of dogs to the toxin of the sea anemone Actinia were surprised to

find that the first injection produced slight or no symptoms while a second injection several days later caused a violent or even fatal reaction To describe this phenomenon of increased reactivity they coined the word *anaphylaxis* to denote the reverse of prophylaxis or protection Since they were using a toxic substance they interpreted the reaction as an increased susceptibility to its toxic effects rather than separate reaction initiated by the first injection However Arthus Theobald Smith and others soon showed that the same type of reaction was readily produced by repeated injection of proteins totally lacking toxicity such as egg white and foreign serum making it clear that the first injection of a harmless antigen sensitized the animal so that a second injection after a suitable interval produced a severe reaction In addition to the general reaction of anaphylactic shock Arthus described the local inflammatory reaction produced by repeated subcutaneous injection of foreign protein generally known as the *Arthus phenomenon*

During the same period the effects of injections of foreign serum were being noted in clinical medicine because of the increasing use of diphtheria antitoxin which had been introduced by von Behring in 1893 The phenomena of delayed serum sickness following the first injection of horse serum and the accelerated reactions following reinjections were accurately described by von Pirquet and Schick in 1905

THE CONCEPT OF ALLERGY

In 1906 von Pirquet introduced the term *allergy* to denote the altered reactivity to infective and antigenic substances resulting from repeated contacts as exemplified by anaphylaxis accelerated serum reactions the tuberculin reaction and the vaccinoid reaction to repeated inoculations of vaccinia virus Both the word allergy and the accompanying concept of specific hypersensitivity acquired through exposure to antigenic agents have received increasing application during the ensuing years

Wolff Eisner in 1906 propounded the theory that hay fever was an anaphylactic phenomenon and Meltzer in 1910 placed asthma in the same group These proposals were not readily accepted by all authorities since hay fever and asthma were known to develop spontaneously in certain individuals apparently predisposed by heredity while anaphylaxis was induced only by injection of antigen but affected essentially all individuals of susceptible species The exact relationship of these diseases to anaphylaxis remains controversial to the present but they are universally accepted as examples of specific hypersensitivity and with the increasing use of the term allergy they have come to be considered prime examples of its clinical manifestations

It has also become apparent that hay fever and asthma are merely two forms of a general type of sensitization producing various disease manifestations in different organs of the body in which the same familial predisposition plays an important part Nonseasonal allergic rhinitis is essentially identical with hay fever except that the causative agent is one to which exposure may take place at any season of the year Infantile eczema and the similar condition of

older children and adults generally termed atopic dermatitis are so frequently associated with hay fever and asthma in the same individual or family that it appears likely the same hereditary predisposition plays a part in their etiology Urticaria and angioedema also show a notable though less close association with hay fever and asthma The same is true of certain gastrointestinal and cerebral reactions to specific foods which are believed to result from allergic reactions localized in the alimentary and central nervous systems classed as gastro-intestinal and cerebral allergy

While the original concept of allergy applied to antigenic agents that is substances inducing antibody formation when injected into experimental animals it was soon evident that substances which did not act as antigens in such tests might also give rise to quite similar sensitization Obermayer and Pick showed in 1906 that the antigenic specificity of proteins might be changed by chemical reactions which introduced such inorganic radicals as nitro and iodine groups On the basis of these observations Wolff Eisner was quick to suggest that nonantigenic agents such as drugs might combine with the body proteins to form complex antigens the specificity of which was determined by the nonantigenic foreign substance This rather tenuous hypothesis was the basis of the *hapten* theory which was fully confirmed some years later by Landsteiner and others and is now the accepted explanation of allergy to drugs and other nonantigenic substances

Contact dermatitis had long been attributed to the direct toxic effects of irritating substances on the skin but it became apparent through the studies of Jadahssohn Bloch and others that a considerable proportion of cases were due to acquired sensitization to substances that produced no effect on the first contact Such familiar and active causative agents as poison ivy were shown to be nonirritating to the skin of persons never previously exposed such as Eskimos and newborn babies However the initial test which gave no reaction at the time caused the development of sensitization in a large number of persons so that a subsequent test two or three weeks later was positive This type of contact dermatitis caused by acquired sensitization was included in the group of allergies The reader should remember that in speaking of *contact dermatitis* as an allergy it is understood that reference is made only to cases involving acquired sensitization and not to those produced by primary irritants The subtsances causing allergic contact dermatitis are generally nonantigenic in the sense that they do not induce the formation of demonstrable antibodies in experimental animals but are considered to act as haptens

Early in the studies of immunology Ehrlich expressed the theory that animals could be immunized only to antigens foreign to their species thus avoiding the reactions that might result from persistent presence of endogenous antigen and specific antibody in the organism a concept denoted as horror autotoxicus However there has subsequently been demonstrated abundant evidence that sensitization may occur not only to antigens of *other individuals* of the same species (*isoantigens* most familar in the blood group antigens) but also to antigens of one s own body (*autoantigens*) The cold hemolysin of paroxysmal hemoglobinuria described by Donath and Landsteiner in 1904 is an

find that the first injection produced slight or no symptoms, while a second injection several days later caused a violent or even fatal reaction. To describe this phenomenon of increased reactivity, they coined the word *anaphylaxis* to denote the reverse of prophylaxis or protection. Since they were using a toxic substance, they interpreted the reaction as an increased susceptibility to its toxic effects, rather than a separate reaction initiated by the first injection. However, Arthus, Theobald Smith, and others soon showed that the same type of reaction was readily produced by repeated injection of proteins totally lacking toxicity, such as egg white and foreign serum, making it clear that the first injection of a harmless antigen sensitized the animal so that a second injection, after a suitable interval, produced a severe reaction. In addition to the general reaction of anaphylactic shock, Arthus described the local inflammatory reaction produced by repeated subcutaneous injection of foreign protein, generally known as the *Arthus phenomenon*.

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stronger support based on histologic evidence was offered by Rich who in 1942 demonstrated lesions essentially identical with those of periarteritis nodosa in human beings allergic to sulfonamide drugs and in rabbits with experimental serum sickness While the analogy is impressive the allergic etiology of clinical periarteritis nodosa cannot yet be considered entirely proved since the actual causative agent has not been demonstrated in any typical spontaneous case of the disease

ALLERGY AS AN ANTIGEN ANTIPODY REACTION

Aside from the physical allergies in which there is no obvious material causative agent all of the conditions cited as examples of allergy show the features generally typical of reactions between antigens and antibodies Allergic reactions show the strict specificity characteristic of such immunogolic reactions Allergy like acquired immunity occurs in certain individuals rather than the species as a whole In many types of sensitization it obviously results from previous contact with the causative agent In allergies developing spontaneously after only normal exposures to allergens the causative relationship of contact to sensitization is less apparent however there is negative evidence of the importance of contact in that patients with multiple sensitizations never react to pollens whose geographic distribution precludes the possibility of previous exposure In those instances where the time of sensitizing contact is clearly apparent the period elapsing before sensitization is established is consistent with the usual period of antibody formation

With the classical methods of demonstrating antibodies the precipitin and complement fixation reactions and the passive sensitization of guinea pigs antibodies could be shown to be associated with only a few allergies such an anaphylaxis serum sickness and the Arthus reaction Prausnitz and Kustner in 1923 showed that the injection of serum from patients with allergies of the asthma hay fever group into normal human skin induced a passive local sensitization of the skin of the recipient The active principle in such serum while lacking the classical properties of antibodies in test tube reactions has come to be generally considered as a skin sensitizing antibody In 1942 Landsteiner and Chase showed that the sensitization of contact dermatitis could be transferred to normal animals by injection of living cells from peritoneal exudates although the serum was without sensitizing activity In 1945 Chase demonstrated the transfer of tuberculin sensitization by the same method As in the case of Prausnitz Kustner phenomenon this transfer of sensitization involved an active principle differing greatly from the known antibodies which had previously been studied only in serum and plasma Despite some theoretical objections this activity of certain cells of sensitized animals and human beings not present in the serum may probably be considered evidence of a cellular antibody Thus as new types of antibodies have been demonstrated by new techniques an increasing proportion of the allergic phenomena have been shown to be mediated by antigen antibody reactions

There are still many reactions which by all clinical criteria are classed as allergic and which it seems reasonable to attribute to antigen antibody reac

tions in which the actual presence of an antibody has not yet been demonstrated. Notable among these are infective asthma urticaria due to infection and most drug allergies. It appears probable that development of new methods may demonstrate some form of antibody mechanism in these cases.

If the term allergy is to have a precise scientific meaning it must be restricted to reactions of similar nature that is to those phenomena of acquired specific sensitization which have *characteristics consistent with those of antigen* antibody reactions even though the antibody may not have been demonstrated in every case. It is in this sense that it will be used in this book.

TERMINOLOGY

In few fields of medicine has nomenclature given rise to more confusion than in allergy. A large number of more or less synonymous terms have been used by different authors and the same words have been employed by some in a broadly inclusive sense and by others with a restricted meaning. Usage in Europe has frequently differed from that prevalent in America and in all countries has changed with time. Thus many European writers have used the terms anaphylaxis and allergy interchangeably while some American authors have restricted the term allergy to human disease and anaphylaxis to experimental sensitizations of animals implying a basic difference between the two groups of phenomena. As will be apparent in the following discussions types and manifestations of sensitization do vary in different species but also and equally with the type of antigen and the route of contact. Since the reaction of a child to repeated injections of horse serum differs from that of an experimental animal no more than the reactions of the guinea pig the rabbit and the dog differ from each other there is no logical reason to apply a different term to it.

In this book an effort will be made to comply with the prevailing usage in current American medical writing but for purposes of clarity it is wise to define the sense in which the more important terms are used realizing that it may not in every case correspond exactly to that of other authors.

Allergy is used as a general term to include all of the phenomena of specific sensitization believed to be mediated by an antigen antibody mechanism whether *such a basis has actually been demonstrated or is the most logical explanation* of the observed characteristics of the reaction. This includes sensitizations of the human species and lower animals resulting from natural exposure to antigen from infection or from artificial procedures. The word has suffered some vagueness of meaning in the past from indiscriminate application to nonimmunologic reactions also to conditions of decreased rather than increased reactivity. Such uses lead only to confusion and are to be discouraged if the most familiar term for the reactions of sensitization is to remain useful.

The terms *sensitization* and *sensitivity* are used interchangeably with allergy in the description of immunologic reactions obviously in other contexts they may apply also to many other nonimmunologic types of susceptibility such as the sensitivity of bacteria to antibiotics. The terms *hypersensitivity* and *hypersensitiveness* are widely used and in medical writings carry an immunologic

connotation but are somewhat cumbersome and redundant and offer no obvious advantage over sensitivity

Anaphylaxis is used in a narrower sense to apply specifically to the type of sensitization resulting from parenteral contact with allergen and manifested by an immediate reaction to similar subsequent contact In addition to experimental procedures clinical sensitization resulting from injections of therapeutic antisera and other medications from insect bites and stings and from the presence of parasites in the tissues falls into this category This limitation leads to some distinctions which may seem at first needlessly precise For example the immediate reaction to injection of horse serum in the patient sensitized by previous injection is classed as anaphylaxis while the clinically identical reaction to the first injection of horse serum into a person susceptible to horse asthma is classed as a general atopic reaction However the distinction is supported by immunologic considerations of the types of antibody involved and the possibility of desensitization

The term *atopy* and the corresponding adjective *atopic* were introduced by Coca and Cooke in 1923 to denote the clinical allergies believed to result from hereditary influences and thought at the time to be peculiar to the human species Prime examples were asthma and hay fever but infantile eczema and certain food and drug idiosyncrasies were also included in the group The immediate wheal reaction to skin tests with the antigen and the Prausnitz Kustner reaction of passive transfer were characteristic of these allergies This classification has been criticized from several aspects The influence of heredity has been questioned by some and is admittedly difficult to demonstrate in many individual cases The concept of a peculiarly human disease has been challenged by later reports of similar conditions in dogs cows and other lower animals Confusion as to the application of the term has also arisen from the demonstration that a considerable proportion of cases of asthma and of urticaria result from infection These sensitizations to infection do not show the immediate wheal reactions to skin tests or the skin sensitizing antibodies typical of atopy yet particularly in children are apparently related to the same hereditary factor Despite these objections the word atopy is a convenient term to designate the typical manifestation of sensitization apparently greatly influenced by hereditary factors showing the wheal reaction on skin test with antigen and with the Prausnitz Kustner type of antibody usually demonstrable in the serum It is used in this book to denote this form of immunologic reaction without implying that the hereditary factor may be established in every case or that the basic mechanism of all cases of asthma or urticaria is the same

In discussions of the delayed form of bacterial allergy the term *tuberculin type* allergy is frequently used since the principles involved are largely based on studies of tuberculosis As previously noted the same type of sensitization has been demonstrated in infections with many different bacteria spirochetes fungi and viruses While much of the information derived from the observation of tuberculosis is believed to be generally applicable to these other infections care is essential in such inferences

The *antibodies* involved in allergic *reactions* are *best designated by* terms descriptive of their observed properties without attempting to define their precise relationships which in some cases are uncertain The typical antibody produced in experimental animals by a suitable course of antigen injections forms a precipitate with the specific antigen fixes complement in the presence of antigen and induces passive anaphylactic sensitization when injected into guinea pigs There is strong evidence to suggest that these three properties of the serum result from the presence of the same antibody

Sera containing such antibody may or may not produce the Prausnitz Kustner phenomenon when injected into normal human skin Sera of allergic animals and human beings may show one or more of these manifestations of antibody activity These will be designated simply as containing *skin sensitizing antibody anaphylactic antibody* or *precipitin* Whether or not these properties are due to the same or different antibodies has not been established in every case The term *reagin* has been widely applied to the skin sensitizing antibody but by its association with atopy has carried implications of heredity and human origin Since similar antibodies may be readily induced in children without the hereditary factor by injections of heterologous serum and in experimental animals the simple descriptive term skin sensitizing antibody seems preferable

The causative agents giving rise to allergic reactions are generally designated as *allergens* Many of these are typical *antigens* and produce an antibody response when injected into experimental animals Others such as drugs and the plant oleoresins causing contact dermatitis are not antigenic when injected into animals but presumably act as *haptens* combining with body protein to form complex antigens the specificity of which is determined by the extrinsic group The term *atopen* which has been applied to allergens producing the atopic type of sensitization is of doubtful value since these substances do not differ in any general characteristics from other allergens

The *shock organs* are the tissues or organs of the body in which the manifestations of an allergic reaction are most apparent for example the nasal mucosa in hay fever

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Chapter 2

IMMUNOLOGY OF ALLERGIC DISEASES

Since the allergic diseases are basically reactions between antigens and anti bodies an understanding of their mechanisms requires a review of the informa tion gained by immunologic studies upon experimental animals and adult human beings From such investigations it is apparent that the development of various types of sensitization depends on the species of animal the hereditary background of the individual the nature of the antigen and the route and intensity of contact After the sensitization is developed the type of reaction to subsequent exposure to the antigen depends on the dose of antigen and the route of contact

ANAPHYLAXIS

General Features—The most completely understood type of allergic reac tion is anaphylaxis in experimental animals which may well be taken as a basis of comparison for the discussion of other forms of sensitization This is exemplified by the classic demonstration in the guinea pig If a normal guinea pig is given a parenteral injection of a nontoxic protein antigen such as egg albumin there is no apparent reaction However if a second injection of the same antigen is given after an incubation period of two weeks there is a violent immediate reaction manifested by restlessness intense dyspnea and death by asphyxia within a few minutes At autopsy the most striking features are a marked constriction of the bronchi which causes obstruction of respiration and emphysema of the lungs resulting from the obstruction It is apparent that the first injection has sensitized the animal so that it reacts to the second in a manner quite different from that of untreated guinea pigs

The *antibodies* involved in allergic reactions are best designated by terms descriptive of their observed properties without attempting to define their precise relationships, which in some cases are uncertain. The typical antibody produced in experimental animals by a suitable course of antigen injections forms a precipitate with the specific antigen, fixes complement in the presence of antigen, and induces passive anaphylactic sensitization when injected into guinea pigs. There is strong evidence to suggest that these three properties of the serum result from the presence of the same antibody.

Sera containing such antibody may or may not produce the Prausnitz-Küstner phenomenon when injected into normal human skin. Sera of allergic animals and human beings may show one or more of these manifestations of antibody activity. These will be designated simply as containing *skin-sensitizing antibody*, *anaphylactic antibody*, or *precipitin*. Whether or not these properties are due to the same or different antibodies has not been established in every case. The term *reagin* has been widely applied to the skin-sensitizing antibody, but by its association with atopy has carried implications of heredity and human origin. Since similar antibodies may be readily induced in children without the hereditary factor by injections of heterologous serum, and in experimental animals, the simple descriptive term skin-sensitizing antibody seems preferable.

The causative agents giving rise to allergic reactions are generally designated as *allergens*. Many of these are typical *antigens* and produce an antibody response when injected into experimental animals. Others, such as drugs and the plant oleoresins causing contact dermatitis, are not antigenic when injected into animals, but presumably act as *haptens*, combining with body protein to form complex antigens, the specificity of which is determined by the extrinsic group. The term *atopen*, which has been applied to allergens producing the atopic type of sensitization, is of doubtful value, since these substances do not differ in any general characteristics from other allergens.

The *shock organs* are the tissues or organs of the body in which the manifestations of an allergic reaction are most apparent, for example, the nasal mucosa in hay fever.

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Physiology —Most of the principal features of anaphylaxis are reactions of smooth muscle and blood vessels the characteristic visible manifestations of the shock in the various species of animals depending on the location of the smooth muscles or vessels which are chiefly affected The asphyxia of the guinea pig is due to intense spasm of smooth muscle of the bronchi the circulatory *collapse and the right heart failure of the rabbit to spasm of the pulmonary* vessels and the splanchnic congestion of the dog to spasm of the hepatic veins

The role of smooth muscle in the reaction is demonstrated by the *Schultze Dale* reaction If a strip of smooth muscle is excised from the intestine or uterus of a sensitized guinea pig and suspended in a water bath addition of a minute amount of the specific antigen to the bath causes a prompt and strong contraction of the muscle The procedure demonstrates the part played by smooth muscle and also that the anaphylactic reaction may take place independently of the circulation and nervous control It is apparent that the sensitization is fixed in the smooth muscle tissue which reacts directly when in contact with the antigen

The vascular and smooth muscle reactions of anaphylactic shock in various species of animals closely resemble those produced by the injection of *histamine* into nonsensitized animals of the same species The same features of shock are inhibited by adequate doses of antihistamine drugs given before the antigen is injected Direct evidence of the release of histamine during anaphylactic shock is given by studies of isolated perfused shock organs and in the intact guinea pig and dog by a significant rise of the histamine content of the circulating plasma during shock

In emphasizing the importance of the reactions of smooth muscles and blood vessels and of histamine in anaphylactic shock it should be pointed out that certain features of anaphylaxis in some species of animals are quite unrelated to their activity *Among these manifestations may be mentioned the loss of coagulability of the blood which occurs in dogs apparently as a result of liberation of heparin and the thrombocytopenia observed in monkeys However neither of these two features is important in anaphylactic shock as observed in the human child*

Antibodies —The devolpment of anaphylactic sensitization is accompanied by the formation of antibodies which are usually readily demonstrated in the circulating blood The serum of an actively sensitized animal or of a child anaphylactically sensitized to horse serum by injection of antitoxin generally forms a precipitate when mixed with the antigen in a test tube and fixes complement in the presence of the antigen These *precipitin* and *complement fixation* reactions are classical manifestations of the presence of antibodies Furthermore the serum of the actively sensitized animal when injected into a normal animal of the same or often other species may produce a state of *passive sensitization* specific for the antigen used to sensitize the first animal Since the guinea pig is very susceptible to passive sensitization the presence of this *anaphylactic antibody* in the serum of human beings rabbits or other species *is generally demonstrated by injection of the serum into the guinea pig There* is abundant evidence that the same typical complete antibody produces all

three types of reaction precipitation complement fixation and passive anaphylaxis However certain sera may show only one or two of these manifestations suggesting the presence of a less complete antibody

The passive sensitization produced by injection of serum from an anaphylactically sensitized animal of another species is usually of brief duration That produced by serum derived from the same species lasts several weeks or months but is far less persistent than active sensitization Passive sensitization has all the typical features of active sensitization and may be demonstrated either by production of shock or by the Schultze Dale reaction

The antibody causing anaphylactic sensitization passes readily through the placenta of the guinea pig so that if a female has been actively sensitized the young born to her are passively sensitized in utero This passive sensitization may persist for a period of weeks but is not transmitted to subsequent generations Sensitization of the male has no influence on the young This passive sensitization in utero is to be clearly distinguished from the hereditary tendency to active sensitization observed in atopy

Desensitization —An animal which has recovered from a severe but not fatal anaphylactic shock does not react to subsequent injections of the same specific antigen for several days *This refractory state or desensitization apparently* results from saturation of the sensitizing antibody with antigen The state of sensitization returns in a few days as new antibody is formed in response to *the shocking dose of antigen The state of desensitization can usually be pro*duced without the occurrence of shock by a series of three or four small injections of antigen at short intervals the individual doses being kept below that required to precipitate shock This is the basis of the method of desensitization employed clinically to permit the administration of antitoxin prepared from horse serum to a child who has been anaphylactically sensitized by a previous injection of the same serum (See Chapter 6)

The Arthus Reaction —If a rabbit is given a series of subcutaneous injections of a typical protein antigen such as egg white the first injection produces no visible reaction After several injections there is an increasingly severe local reaction at the site of each with edema and ecchymosis progressing to necrosis of the tissues This Arthus reaction is in a sense the local counterpart of general anaphylactic shock

The development of this type of sensitization is also accompanied by the formation of precipitating antibodies in the circulating blood The degree of local reaction is closely correlated with the amount of circulating antibody Injection of serum containing adequate amounts of precipitating antibody into normal rabbits or guinea pigs produces passive sensitization of the Arthus type

Occurrence of this reaction apparently depends upon the presence of blood vessels as it cannot be reproduced in tissue cultures of cells from sensitized animals or in avascular tissues such as the cornea of the eye Microscopic observation of the living tissues by Abell and Schenck showed the initial reaction to take place in the small vessels Within a few minutes after the injection of antigen into the tissues of the sensitized rabbit the blood flow in the adjacent vessels is slowed and leukocytes adhere to the walls of the vessels The vascular

walls disintegrate and first leukocytes and then plasma and red cells escape into these tissues Over a period of a few hours this becomes apparent macroscopically as a hemophagic edematous area increasing in intensity for one or two days and often progressing to necrosis

ATOPIC SENSITIZATION

The atopic group of familial allergic diseases including asthma hay fever infantile eczema and urticaria consists in general of reactions of the immediate type Some of the manifestations of these diseases resemble those of anaphylaxis for example bronchial asthma closely resembles anaphylactic shock in the guinea pig However many differences in immunologic aspects are apparent on careful consideration

The atopic diseases are primarily diseases of the human species For many years atopic disease was believed to be limited entirely to man but more recently similar manifestations of sensitization have been described in dogs cattle and other species

Atopy differs from anaphylactic sensitization in the strong familial or hereditary tendency which predisposes to its development Essentially all guinea pigs are anaphylactically sensitized by a suitable injection of antigen but not more than 10 per cent of the human population appear to be susceptible to atopic disease The frequent association of several atopic patients in the same family lends support to the presence of a hereditary tendency A child who has manifested the atopic tendency by symptoms of one disease of the group is very likely to develop other forms of the sensitization

The means of acquiring sensitization also differs greatly The development of anaphylactic sensitization always follows an intense usually artificial exposure to antigen most often by parenteral injection In the development of atopic disease the child who is predisposed by heredity becomes sensitized spontaneously after the same natural exposures to antigens that are experienced by others in his environment No special exposure or injection is needed On the other hand in the case of a person without the inborn susceptibility to atopy no degree of exposure produces sensitization If the pollen antigens which are most active in causing atopy are injected into normal persons sensitization is not produced although the person may react by forming the immune type of blocking antibody which is developed during the injection treatment of allergic patients (See Chapter 7) Atopy may be considered the reaction of an abnormal immune mechanism to natural exposures to antigen while anaphylaxis is the reaction of a normal immune mechanism to an artificially imposed unnatural exposure to antigen

The serum of the atopic person does not show the precipitin or complement fixation reactions with the specific antigen which are associated with anaphylaxis nor does it induce passive anaphylaxis when injected into guinea pigs It does have the property of producing passive sensitization in the normal person If a considerable quantity of blood is transfused from an atopic person to a normal person systemic sensitization lasting several weeks is transferred

If a small amount of the atopic serum is *injected into the skin of a normal* person the *Prausnitz Kustner phenomenon* of local passive sensitization is produced. For a period of three or four weeks skin at the site of injection reacts to the specific antigen like the skin of the person whose serum was injected. This property of passive sensitization reflects the presence of skin sensitizing antibody *in the serum. However the presence of this antibody can be demon*strated only by the reaction it produces in living human tissues it does not sensitize guinea pigs or react in the test tube with the antigen. By means of the precipitin test and the passive sensitization of guinea pigs the serum of a child who has been anaphylactically sensitized to horse serum by injection of *antitoxin may be readily distinguished from that of a child atopically sensitive* to horse protein who has not received previous injections of the antigen.

Unlike the anaphylactic antibody of guinea pigs the skin sensitizing antibody of atopic human beings does not pass through the placenta consequently children of an atopic mother are not passively sensitized to the same allergen. On the other hand the familial incidence of atopic disease apparently results from inheritance on a genetic basis equally from the father and the mother of a tendency to acquire active sensitizations to environmental antigens.

If desensitization by injections of the specific antigen is attempted the *differences between atopy and anaphylaxis are again apparent. The rapid desensitization* by three or four injections of antigen which is usually possible in anaphylaxis cannot be accomplished in atopy. Injections of antigen do not reduce the amount of circulating skin sensitizing antibody but over a period of time stimulate the formation of a specific blocking antibody which combines with the antigen and thus may inhibit its reaction with the skin sensitizing antibody. The effect of the antigen injections is more one of immunization than desensitization. For details see Chapter 7.

Many of the physiologic manifestations of atopic sensitization like those of anaphylaxis resemble the effects of histamine and appear to result from its liberation by the antigen antibody reaction. For this reason the striking similarities in symptomatology need not be taken as evidence of an identical immunologic mechanism. This should be kept in mind when attempting to *draw analogies between these two types of sensitization.*

CONTACT DERMATITIS

In contact dermatitis the manifestations of sensitization differ greatly from those of anaphylaxis. The reaction is delayed twelve to twenty four hours or more after exposure to antigen is usually local rather than general and is characterized by a slowly developing and slowly resolving inflammation of the *skin rather than a quickly reversible reaction of the smooth* muscles and blood vessels. However in many of the features of its development contact dermatitis strikingly resembles anaphylaxis. Like anaphylaxis contact dermatitis is readily produced in experimental animals particularly guinea pigs. When a suitable sensitizing agent is applied to the skin of a normal pig there is no visible reaction. However in the course of a *week or two* active sensitization is de

veloped and a second application of the same allergen produces a definite dermatitic reaction The sensitization shows the same degree of specificity as other allergic reactions As in anaphylaxis the development of sensitization must be considered the normal response to the conditions imposed as practically 100 per cent of guinea pigs may be experimentally sensitized with suitable active chemical agents such as picryl chloride

One of the marked differences between the two types of sensitization is in the types of substances producing them While anaphylaxis is produced mainly by typical protein antigens contact sensitization is rarely caused by protein It may be caused by many different types of substances but mostly by chemically active compounds of relatively simple structure and low molecular weight In experimental studies various halogenated benzene compounds such as dinitrochlorbenzene and picryl chloride are employed as allergens These same substances are important causes of human dermatitis among workers in chemical industry but in pediatric practice the most important contact agents are the catechols which are the active principles of poison ivy and sumac None of these contact allergens are antigenic if injected into experimental animals presumably they act as haptens by combining with the proteins of the skin

The effective route of sensitizing contact is also different The development of anaphylactic sensitization depends upon the allergen passing beyond the barriers of skin and mucosa and is most readily accomplished by deep parenteral injection Contact sensitization, on the other hand depends upon the allergen coming into contact with the superficial layers of the skin and is effectively produced by application of the allergen to the surface of the skin or by intracutaneous injection but not by injection deep into the tissues

No antibodies are demonstrable in the sera of patients or experimental animals with contact dermatitis and the sera do not passively sensitize normal animals However in experimental contact dermatitis the sensitization may be transferred to normal animals by injection of lymphocytes from actively sensitized animals This cellular transfer is apparently evidence of a type of antibody activity present in the cells but not the serum

DELAYED BACTERIAL HYPERSENSITIVITY

The tuberculin reaction is the most familiar and the most completely studied example of the delayed allergic reaction induced by infection with many different bacteria fungi and viruses The development of such sensitization ordinarily results within two to three weeks after infection with living organisms After the sensitization is complete reactions may be elicited by the injection of living bacteria dead bacteria or tuberculin which is a protein derived from the bacillus However injections of tuberculin or other proteins derived from the organism into normal animals do not produce the characteristic delayed type of sensitization Injection of living bacilli or of massive doses of killed bacilli is necessary Raffel has shown that a lipoid wax present in the organism which is not by itself antigenic must be injected in conjunction with the tuber

culoprotein which is the actual antigen in order to stimulate the development of tuberculin sensitization When typical protein antigens other than tuberculoprotein for example egg albumin which characteristically induce anaphylactic sensitization are injected in conjunction with the same wax fraction a delayed type of reaction to the specific antigen is induced Thus the characteristic delayed reaction is related more to the mechanism of sensitization than to the particular antigen used

The delayed allergic reaction differs from the anaphylactic and atopic reactions in that it involves the reaction of individual cells rather than special tissues such as smooth muscle and blood vessels When cells from sensitized animals are grown in tissue culture the successive generations of cells retain the property of reacting to the specific allergen Similar cultures of cells from anaphylactically sensitized animals show no reaction to their specific antigen

This type of delayed allergic reaction is not related to the presence of any specific antibody in the circulating blood and the plasma or serum of the actively sensitized animal does not induce passive sensitization in normal animals In experimental tuberculin sensitization the specific reaction may be transferred from actively sensitized to normal animals by the injection of suspensions of lymphocytes and monocytes in the same manner as the transfer of contact sensitization This suggests the presence of a similar type of cellular antibody

The characteristic feature of delayed bacterial sensitization is injury to or necrosis of cells exposed to the antigen There is nothing to suggest that histamine plays a part in the reaction and its occurrence is not influenced by antihistamine drugs

CLASSIFICATION OF ALLERGIC REACTIONS

The most useful working classification of allergic phenomena is that based on immunologic features since these are related to the basic mechanism In

TABLE I

IMMUNOLOGIC CLASSIFICATION OF ALLERGIES

I *Immediate reactions Associated with circulating antibodies*
- A *Anaphylactic type* Readily induced experimentally in susceptible species Heredity a negligible factor Associated with precipitating complement fixing and anaphylactic antibodies
  - 1 Anaphylactic shock
  - 2 Arthus reaction
  - 3 Serum sickness
  - 4 Anaphylactic sensitization to parasites
- B *Atopy* Not readily induced experimentally Heredity a major factor Associated with skin sensitizing but not precipitating or anaphylactic antibodies
  - 1 Hay fever
  - 2 *Asthma (extrinsic type)*
  - 3 Urticaria (due to extrinsic allergens)
  - 4 Infantile eczema and atopic dermatitis
  - 5 Gastrointestinal allergy
  - 6 Cerebral allergy

II *Delayed reactions Associated with cellular antibodies*
- A *Contact dermatitis* Readily induced in susceptible species by contact of skin with nonliving agent
- B *Delayed (tuberculin type) allergy to infective agents* Not readily induced by contact with antigen Generally results from infection with living agent

general sensitizations associated with circulating antibodies are manifested by immediate reactions and those associated with cellular antibodies by delayed reactions In both of these groups further subdivisions may be made on the basis of the mode of acquiring sensitization (Table I)

Allergies in which the antibodies have not been demonstrated can be included in the classification only by inference Thus urticarial reactions to penicillin which clinically resemble serum sickness may be tentatively placed in the anaphylactic group and dermatitis medicamentosa which sometimes shows a positive patch test to the causative drug in the contact dermatitis group Definite classification of infective asthma and urticaria due to infection both of which have the clinical but not the immunologic features of atopy is difficult

An attempt to establish a rigid classification is not essential It is more important to realize that the manifestations of allergy in children may take many forms depending on (1) the hereditary background (2) the nature of the allergen and (3) the route and intensity of exposure

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Chapter 3

NONIMMUNOLOGIC FACTORS AFFECTING ALLERGIC REACTIONS

Since the clinical manifestations of allergic disease are those of comp physiologic and pathologic phenomena resulting from the union of antigen a antibody in the tissues the reactions may be affected by various changes in physiologic state of the body The tone of the blood vessels and smooth mu which are involved in many of these allergic phenomena particularly the ato and anaphylactic reactions is regulated by the interaction of the sympathe and parasympathetic divisions of the autonomic nervous system and is also in enced by the secretion of hormones and by the chemical composition of the b fluids Through the medium of the autonomic nerves and hormones the t may also be affected by changes in activity of the body by emotional s While histamine and possibly other toxins released by the allergic reaction directly on the vessels and smooth muscles the physiologic factors which regu the tone of these tissues may affect the degree of response to a given antige stimulus or even its occurrence

CHEMICAL FACTORS

Mineral Salts —Numerous physiologic experiments have shown that the to and *permeability* of blood vessels and the excitability of nerves and muscles influenced by the *relative* concentrations of various cations in the body bathing them Calcium ion tends to lessen the irritability of nerves and and *to decrease* the permeability of capillaries these actions being to some extent by *potassium* and magnesium ions Calcium tends to reactivity of *parasympathetic* nerves and potassium that of sympatheti

Because of these actions several of the earlier workers in the field have suggested that allergic disease might be related to a deficiency of calcium or of its active ionized form in the plasma and tissue fluids On this basis the therapeutic use of calcium salts for treatment of allergic disease was advocated However more careful analyses have shown that the plasma of patients with uncomplicated allergic disease contains essentially normal amounts of calcium of ionized calcium and in fact of all the major cations The supposed therapeutic effects of supplementary calcium have proved to be negligible and with the introduction of more rational pharmacologic agents such as the antihistamines its use has been abandoned None of the other physiologically active salts have proved important in therapy The development of extensive allergic edema such as occurs in severe serum sickness obviously involves retention of salt and water However control of their intake does not appreciably affect its occurrence or severity nor are the ion concentrations in the plasma altered

Attention has also been directed toward the acid base balance in allergic disease and some early studies indicated the occurrence of a mild alkalosis A decrease in the acidity of the gastric juices was also reported Both of these hypotheses have subsequently been proved erroneous and attempts to treat allergic disease with hydrochloric acid both by mouth and intravenously were ineffectual Other authors advocated the use of a ketogenic diet to increase the acid balance As in the case of calcium therapy the favorable reports were not reproducible and the use of acidifying measures has fallen into disuse

Vitamins—During the period of discovery and study of the vitamins attempts have been made to relate allergic reaction to deficiencies of various vitamins and to use these agents in therapy Vitamin C has been the most widely used but the most careful studies indicate that the blood of allergic persons contains normal amounts of this vitamin and that even large doses have no therapeutic effect The use of vitamin D in very high dosages bordering on toxicity has also been advised but never has been adequately proved to exert an effect commensurate with the dangers of renal disease which are involved

On the whole no deficiency of minerals or vitamins has been shown to have a specific influence on allergic disease and no therapy based on these factors has stood the test of time Their only practical importance in relation to allergic diseases of children is the need of insuring an adequate supply for normal growth and development when the diet is radically altered in attempts to eliminate allergenic foods This is readily accomplished by the use of concentrated supplements

HORMONES

The hormones most obviously affecting allergic reactions are those of the adrenal gland one of whose chief functions is that of adapting the body to various forms of stress Excision of the adrenal glands from experimental animal greatly increases their susceptibility to anaphylactic shock and this effect may be controlled by injection of adrenal hormones to replace the normal supply However there is little evidence to suggest that allergic patients suffer from

deficiency of the adrenal hormones Clinical adrenal insufficiency Addison s disease is rarely associated with allergy and studies of the excretion of adrenal cortical hormones by allergic patients have in general shown essentially normal values The doses of cortisone required to relieve allergic disease are usually larger than those needed to control adrenal insufficiency showing that the therapeutic effects result from an excess of hormone rather than correcting a deficiency Further evidence that the adrenal cortex of allergic patients is capable of normal function is shown by the observation that effects of stimulation of the adrenal cortex by corticotropin are identical with those of exogenous cortisone or hydrocortisone

Adrenal Medulla—Epinephrine the principal hormone of the adrenal medulla has a prompt and powerful effect on blood vessels and smooth muscle paralleling the effects of sympathetic nerves and antagonizing the effects of the parasympathetic In general it antagonizes the actions of acetylcholine and to a lesser extent those of histamine The administration of exogenous epinephrine relieves symptoms of allergic rhinitis bronchial asthma and urticaria In adequate doses it inhibits to some degree most of the principal manifestations of anaphylactic shock The effects of endogenous secretion of epinephrine are so closely intermingled with the effects of sympathetic nerve control that a clear differentiation is usually impossible However the effect of their combined action is occasionally apparent when extreme fear or nervous shock produces prompt but temporary relief of chronic allergic disease of the respiratory system Epinephrine is without significant effect on the delayed inflammatory types of allergy typified by contact dermatitis and the tuberculin reaction For details of the therapeutic use of epinephrine and related drugs see the following chapter

Adrenal Cortex—The adrenal cortical hormones also have profound effects on many allergic reactions These are manifested after the administration of exogenous hormones *cortisone* or *hydrocortisone* or stimulation of secretion of endogenous hormones by injection of *corticotropin* the pituitary adrenocorticotropic hormone In experimental sensitization allergic phenomena may be affected either by the effects on antibody formation and resultant sensitization or by effects on the reaction of the already sensitized animal to contact with the antigen In human sensitization only the effect on the reaction is of practical importance

Careful studies of antibody formation in rabbits indicate that both cortisone and corticotropin administered during the period of sensitization decrease the quantity of antibody produced by a given antigenic stimulus Presumably as a result of less active antibody formation various allergic reactions in the *actively* sensitized animal are inhibited by these hormones if given during the period of sensitization This applies to the Arthus reaction in rabbits experimental encephalomyelitis in monkeys and the arteritis of serum sickness in rabbits Studies of the effect of these drugs on antibody formation in man are less conclusive careful quantitative measurements showing no significant inhibition by the usual doses

Once sensitization is accomplished either actively or passively administration of cortisone or corticotropin before contact with the antigen has no significant effect on the Arthus reaction of the rabbit or anaphylactic shock in the guinea pig On the other hand the asthmalike symptoms of bronchial constriction which follow inhalation of antigen by the anaphylactically sensitized guinea pig are decreased In the mouse adequate doses of cortisone inhibit anaphylactic shock due to injected antigen The effects of corticotropin and cortisone in human anaphylactic shock have not been adequately established but the severe reactions which have occasionally resulted from sensitization to corticotropin itself cast grave doubts on their efficacy in acute anaphylaxis Serum sickness in human beings is generally relieved

Essentially all of the atopic diseases are markedly inhibited by cortisone hydrocortisone and corticotropin Their effects on severe asthma atopic dermatitis and allergic rhinitis generally exceed those of all other agents These benefits however are palliative rather than curative and in severe chronic disease symptoms tend to recur promptly when the treatment is stopped While the actual symptoms are inhibited by adequate doses of the drug the skin reaction to antigen or histamine is not appreciably affected and the titer of skin sensitizing antibodies in the circulating plasma is unchanged The mechanism of action remains obscure The practical aspects of therapeutic use are discussed in Chapter 4

The delayed forms of allergic reaction which are not affected by epinephrine are diminished by the adrenal cortical hormones Contact dermatitis is usually promptly relieved by adequate doses The tuberculin reaction in the guinea pig is inhibited Long and Favour reported similar inhibition of the tuberculin reaction in human patients receiving relatively large doses of cortisone or corticotropin over periods of three or four weeks With smaller doses and shorter periods of treatment the reaction is not usually affected Thus it is apparent that the administration of exogenous adrenal cortical hormones or the artificial stimulation of the endogenous supply by corticotropin has notable effects on a wide variety of allergic manifestations The extent to which changes in the natural secretory activity of the adrenal cortex affect allergic disease is less clearly established However it is well known that certain conditions of stress such as acute febrile infectious disease major operation and severe trauma are frequently followed by remissions of chronic asthma or atopic dermatitis Since an increased secretion of cortical hormones results from such stress it is the probable mechanism of the remission of the allergic symptoms

THE AUTONOMIC NERVOUS SYSTEM

Most of the shock organs involved in anaphylactic and atopic reactions are innervated by the autonomic nervous system and under the joint control of its sympathetic (thoracolumbar) and parasympathetic (craniosacral) divisions The efferent impulses of the two divisions produce antagonistic effects on the organs supplied the parasympathetic division producing the effects of acetylcholine and the sympathetic division effects similar to those of epinephrine The tonus of small arteries and arterioles and of smooth muscle in the various

organs apparently depends upon the balance of impulses received through the two components of their dual innervation The actions of histamine occur independently of the nerve control *but to a considerable extent parallel those of the parasympathetic division which produces constriction of bronchial muscle dilation of small blood vessels flushing of the skin and secretion of the mucous glands of the respiratory system It is apparent that the effects of the parasympathetic nerves are in many instances synergistic with the changes taking place in anaphylactic and atopic reactions while those of the sympathetic nerves are generally antagonistic As pointed out in the previous chapter manifestations of the anaphylactic and tuberculin types* of allergy can occur independently of the autonomic nervous system and predominance of evidence indicates it does not play an essential role in allergic reactions However there are many indications that its influence may augment or inhibit reactions to allergens

If the mucosa of one side of the nose is deprived of sympathetic control by operative means or by blockage of the stellate ganglion with a local anesthetic the initial reaction is one of hyperemia edema and increased mucus secretion quite similar to allergic rhinitis If the procedure is carried out on a person allergic to pollen the reactivity of the mucosa on the denervated side to the specific antigen is found to be greatly enhanced as compared to the other side Thus the degree of allergic reaction to a given antigenic stimulus may be affected by disturbing the normal control of the autonomic nervous system

Stimulation of the parasympathetic vagus nerve in experimental animals causes a constriction of the bronchi somewhat analogous to asthma In operative procedures on the autonomic nervous system for the relief of chronic asthma various surgeons have reported observations of blocking and of stimulating both the sympathetic and vagus nerves to the bronchi The results have been confusing Apparently the largest percentage of good therapeutic results have followed operations in which the entire network of autonomic nerve fibers to the bronchi was excised but the failure of even this procedure to produce consistent relief of asthma is evidence that the autonomic nerves are not the essential mechanism of the disease The degree of benefit in some cases may perhaps be considered evidence that the autonomic nervous system was a contributory factor in the occurrence or aggravation of symptoms

The effects of administration of acetylcholine or its derivative Mecholyl are identical with those of stimulation of the parasympathetic nerves. If Mecholyl is given to a patient susceptible to asthma but free of symptoms at the time its effect is to produce bronchial constriction which may be inhibited by atropine Similar doses have no similar effect on persons who are not naturally affected by asthma This apparent elicitation of latent asthma is consistent with the view that the parasympathetic nervous system may produce similar effects in patients who are susceptible to the disease

From the evidence available one may logically assume that while the autonomic nervous system does not play an essential part in the mechanism of atopic disease or anaphylaxis its effects may alter the reactivity of the shock organ so that the allergic phenomena are enhanced or inhibited

* Evidence that th also t of atopic reactions is given Chapter

EFFECT OF PHYSIOLOGIC ACTIVITY OF THE SHOCK ORGAN

Since individuals with the tendency to atopic sensitization readily acquire allergy to new antigens with which they are in contact many of them are somewhat allergic to a large number of common substances to which they are exposed most of the time This may keep the shock organ in a persistent state of mild allergic reaction even during periods when there are no obvious symptoms of allergic disease This latent allergy is often apparent in the appearance of the nasal mucosa of a child with allergic rhinitis if examined at a time when no symptoms are noted Auscultation of the chest of a child subject to asthma often reveals a few sibilant rales when the patient is perfectly comfortable

During this state of latent allergy changes in the physiologic activity of the shock organ may increase the allergic reaction to produce symptoms Thus in latent asthma any increase in the pulmonary ventilation may induce audible wheezing This may follow voluntary overbreathing or increased respiratory effort in sighing laughing audibly singing or physical exercise Eczema may be aggravated by increased sweating due to any cause In the child subject to urticaria increased blood flow to the skin induced by a hot bath emotional blushing or physical exertion may precipitate a fresh crop of wheals

EFFECT OF NONSPECIFIC IRRITANTS ON THE SHOCK ORGAN

During the state of latent allergy described in the previous section the shock organ is also excessively reactive to nonspecific irritants Substances and physical changes which do not induce specific allergic sensitization and which are only mildly irritating to normal children may precipitate a reaction in the allergic shock organ indistinguishable from that induced by exposure to the specific antigen Among the agents commonly producing this type of attack in the respiratory passages are cold damp air smoke fumes of fresh paint turpentine and other volatile chemicals and nonantigenic mineral dusts In children allergic to extrinsic allergens an exacerbation may be caused by an acute cold Allergic diseases of the skin may be aggravated by excessive heat chapping of the skin by cold wind by fuzzy woolen garments even though the child is not specifically allergic to wool and most important by scratching

These nonspecific irritants play an important part in precipitating attacks in the child who is already allergic but it is essential to distinguish them from the actual antigens which initiate the underlying sensitization Attempts to do skin tests with nonspecific irritants are futile

INFLUENCE OF EMOTIONAL FACTORS

At the end of the nineteenth century most of the diseases now classed as manifestations of atopic sensitization were considered neuroses a classification which at the time carried little hope of constructive therapy When the application of allergic method of diagnosis and treatment greatly improved the handling and prognosis of these conditions the neurosis hypothesis was largely forgotten More recently due both to the realization that not all patients with these diseases respond well to the allergic approach and to the active application of

Freudian psychiatry to psychosomatic medicine interest in the role of emotional factors in allergic disease has greatly increased

Much of the literature on this subject is descriptive of relatively uncontrolled observations and in many of the reports dealing with emotional factors little or no mention is made of allergic factors so that it is not always clear whether the reactions described are aggravations of pre existing allergic disease or phenomena occurring in patients without the allergic background Among the more carefully controlled studies is that of Holmes Goodell Wolff and Wolff who observed 100 patients with vasomotor rhinitis many of whom had other evidences of allergy repeatedly under varying conditions of emotional stress They found that feelings of frustration anger insecurity and embarrassment arising out of interpersonal relationships tended to increase the swelling and secretion of the mucosa On the other hand in a few instances panic or dejection caused pallor and dryness of the mucosa with shrinkage of the turbinates Thus the vasomotor change which at least in some instances had an allergic background might be either aggravated or inhibited by emotional reactions Graham and Wolff described the rapid appearance of fresh lesions of urticaria during emotional stress experimentally produced under controlled conditions during psychiatric interviews

There is ample evidence that the emotions exert powerful effects on the autonomic nervous system as exemplified by emotional blushing pallor sweating sighing crying and nausea There is little doubt that they may also influence the secretion of adrenal hormones The influence of emotions on the secretion of epinephrine has been extensively studied in the cat by Cannon and may be presumed to play a part in human beings although differentiation between the hormonal effects of epinephrine and the nervous effects of the sympathetic system is rarely possible The effect of emotional stress on adrenal cortical secretion is suggested by the report of Thorne that during a college crew race the coxswain and coach showed evidences of increased adrenal cortical secretion similar to those of the oarsmen who actually rowed four miles

As has been previously pointed out in the patient with allergic disease changes in physiologic activity or blood flow in the shock organ such as those produced by emotions through the autonomic nervous system may markedly affect the occurrence or severity of symptoms Most often these stimuli tend to augment the allergic response or to produce active symptoms in a patient whose allergic disease has been latent However they may occasionally have the opposite effect as described by Holmes and his associates in the nasal mucosa during panic and dejection These variations in the response of allergic symptoms to emotional stress are difficult to explain but no more so than the manifestation of anger in one person by flushing of the face and in another by extreme pallor Presumably stimulation of the parasympathetic system tends to augment allergic symptoms and stimulation of the sympathetic system or the adrenal gland to inhibit them

A great deal of study has been devoted to the psychodynamic mechanisms which tend to bring out allergic symptoms Dunbar described a specific personality type subject to asthma while French and Alexander found asthma to

occur in persons of extremely varied personality traits but felt that the basic factor was an excessive dependence on the mother Symptoms of asthma were found to be precipitated by events which involved or threatened separation from the mother the attack representing a suppressed desire for love and protection This view has been developed into the idea that asthma in children results largely from rejection of the child by the parent On the other hand some workers in the field have felt that separation of the child from the parent in an institution parentectomy is a highly favorable procedure in removing emotional stress and treating chronic asthma Psychiatrists using the analytic approach have described different psychodynamic mechanisms in other types of allergic disease such as eczema and urticaria but have been unable to agree on a specific type of conflict as the basis of each disease

Without attempting to evaluate or reconcile these somewhat contradictory psychiatric viewpoints the present authors feel that the factor of parental rejection has been overstressed and that attempts to establish a single psychodynamic mechanism in asthma or any allergic disease are futile In so far as asthma is affected by the emotions it is felt that any stress or conflict sufficiently strong to discharge the necessary autonomic nervous impulses or hormonal changes may influence the occurrence and the severity of symptoms in a child with latent asthma Because of the family relationship most emotional stress in childhood is related to the parent or guardian who in early life stands between the child and the outside world and also mediates conflicts between siblings within the family Even in adolescence the attitudes of the parent continue to influence greatly the child s emotional reaction to outside contacts

In practice any type of emotional conflict whether due to neglect or emotional rejection by the parent to undue solicitude and demand for too close a relationship to the parent to constant pressure for accomplishment by the child or to an unsatisfactory acceptance by other children seems to play an equal part The psychiatric logic which tends to interpret excessive parental zeal and overpossessive love as a compensatory reaction to conceal a basic subconscious rejection is not convincing to one without training in this system of reasoning

From the practical standpoint one should bear in mind that emotional factors may play a part in the production of allergic symptoms but that their importance has been overemphasized in much of the recent literature and that they apparently act as precipitating causes of attacks in children whose underlying allergic state results from sensitization to extrinsic allergens or infections The recognition of real emotional stress should aid in the handling of patients but preoccupation with the psychic aspects should not lead to neglect of the diagnosis and treatment of the basic immunologic factors causing the sensitization

Due consideration must also be given to the effects of serious and persistent allergic disease on the behavior and emotional reactions of both the child and his parents Recurrent attacks of severe asthma which may constitute as great an obstacle to normal life as heart disease or epilepsy are a natural cause of anxiety to the entire family Likewise an older child disfigured by chronic

atopic dermatitis and tormented by constant itching faces a difficult adjustment to life and interpersonal contacts which is often reflected in personality changes When confronted with a child showing both severe allergic disease and poor emotional adjustment care is necessary in deducing relationships of cause and effect

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Chapter 4

DRUGS USED IN THE TREATMENT OF ALLERGY

Classification of Antiallergic Drugs —There are three main groups of drugs which are applicable to a sufficient variety of allergic conditions to be considered antiallergic These comprise (1) the *antihistamine* drugs which are effective in a considerable number of atopic and anaphylactic diseases producing their effect by blocking the action of histamine which is released as an intermediary in the reaction (2) the *adrenergic* drugs of the epinephrine group which are effective in atopic and anaphylactic conditions because of an action paralleling that of the sympathetic nervous system which inhibits these reactions and (3) the *adrenocortical* and *corticotropic hormones* and their derivatives which inhibit a wide variety of both immediate and delayed allergic reactions through a mechanism not clearly established

A great many other drugs which cannot be classed as specifically antiallergic are useful for relief of symptoms of various allergic diseases These are discussed under the treatment of each disease

ANTIHISTAMINE DRUGS

A large number of drugs blocking the action of histamine on the tissues have been synthesized of which several dozen have been placed on the American market Because of this wide choice of agents many of which are quite similar in pharmacologic action no attempt will be made to discuss all those available but merely to mention a few which have proved useful without implying that they are necessarily superior to those omitted Since few of these drugs have been marketed by more than one manufacturer their proprietary names have

been popularized and their official names are rarely used Therefore the more familiar proprietary names are used in this book

These drugs have a variety of chemical structures The majority fall into three groups (1) *ethylenediamine derivatives* Pyribenzamine Antergan Phenergan Histadyl and Neohetramine (2) *ethanolamine derivatives* Benadryl Ambodryl and Decapryn and (3) *monamines* Trimeton and Chlor Trimeton Thephorin Perazil and Antistine have chemical structures which do not fall into any of these three main groups

All of these drugs have a more or less potent antihistamine effect which is readily demonstrable in pharmacologic studies on experimental animals and human beings Because of this action they are useful in the symptomatic relief of allergic rhinitis especially seasonal hay fever and urticaria They have an inhibitory effect on anaphylactic reactions and the constitutional reactions of atopic children to overdoses of injected allergens but are less rapid in their action than epinephrine which should be used first in severe general allergic reactions The antihistamine drugs when used alone are relatively ineffective in the control of asthma but are of some value in combination with ephedrine or aminophylline The combination of diphenhydramine and aminophylline marketed as Hydryllin is an effective oral medication for mild asthma particularly useful in children who tolerate ephedrine poorly The antihistamine expectorant compounds are useful for asthmatic cough and bronchitis

The drugs of this group have no curative effect on the lesions of eczema and contact dermatitis but help to lessen itching and therefore scratching when administered systemically or topically This effect apparently depends on the local anesthetic action common to most of the group rather than the actual antihistamine effect The topical use of any antihistamine drug involves risk of sensitization to the drug

Practically all of these drugs have some cerebral effect which is primarily sedative or depressant but may be manifested by excitement or confusion Extreme overdosage in cases where infants have swallowed large numbers of pills usually produces cerebral stimulation convulsions and respiratory depression occasionally fatal The sedative effect of moderate doses which is most marked in the case of Phenergan Benadryl and Decapryn is usually considered an undesirable side effect However it has advantages in the case of children who are suffering from severe urticaria or serum sickness and for use at bedtime in any case where allergic symptoms interfere with sleep For the treatment of mild symptoms during the daytime the less sedative drugs such as Chlor Trimeton and Ambodryl are preferable

Another side effect which is sometimes troublesome is nausea To avoid this the drugs are best given after meals If this is not effective one should change to another drug of the group

The antihistamine drugs are readily adsorbed when given by mouth and this is the usual route of administration The effects are usually apparent within a half hour and in most cases last about four hours but the effect of Phenergan is longer or about eight hours Several other drugs of the group are

supplied in slowly adsorbed or delayed action forms in order to prolong the effect of a single pill or capsule. Since allergic symptoms are often present only intermittently during the day or night maintenance of a continuous action through the twenty four hours is not always essential or desirable. In general the medications may be prescribed to be used only as necessary. Somewhat quicker and possibly stronger effects may be obtained when necessary by the intramuscular injection of sterile solutions in which several of the drugs are also supplied.

There is no one antihistamine drug which is outstanding in its ratio of potency to toxic effects. In general the more potent drugs of the group are also more likely to produce drowsiness or nausea. However different children vary in their susceptibility to these side effects and the choice of drug for the individual is often a matter of trial and error. The various drugs may be roughly classified according to potency and incidence of toxic effects as an aid in choosing the drug most suitable for the particular child. If the allergic symptoms are severe one may first try one of the more potent drugs and change only if the side effects are troublesome. For the relief of milder symptoms it may be well to start with a drug of moderate potency and less tendency to toxic actions changing to one of the more potent group if the first is not effective (Table II).

TABLE II RELATIVE POTENCY AND TOXICITY OF VARIOUS ANTIHISTAMINE DRUGS

1 *Highly Potent and Highly Sedative*
Phenergan
Benadryl
Decapryn
2 *Potent but Less Sedative*
Pyribenzamine
Tagathen
Neo Antergan
Ambodryl
3 *Moderately Potent Less Sedative*
Chlor Trimeton (Teldrin)
Perazil
4 *Less Potent Side Effects Minimal*
Neohetramine
Thephorin

Phenergan is apparently the most potent and has the longest duration of action

Intensive use of antihistamine drugs over a period of several months involves a slight risk of the development of leukopenia. Such cases have been reported after the use of several drugs of the group. The largest number was after use of Pyribenzamine but this may simply reflect the fact that it has been one of the most widely used drugs of the group. More frequently prolonged use of one drug results in its becoming decreasingly effective while other drugs of the group are still effective in the same child. For both of these reasons continuous use of full doses is to be avoided if possible but when this is necessary it is well to change after a month or two to another drug with a different chemical base and to count the leukocytes periodically.

The dosage of antihistamine drugs in children of 10 to 12 years is essentially the same as the average dose for adults. The tablets and capsules listed below

in general contain an average adult dose Some of the tablets are scored to permit half dosage The preparations designed for prolonged action contain 2 or 3 doses so prepared as to be adsorbed over a period of 8 to 12 hours

The frequency of dosage will depend on the illness If continuous action is desired the dose must be repeated every 4 to 6 hours except in the case of Phenergan and the various preparations intended for prolonged action which may be given every 8 to 12 hours However in many allergic diseases symptoms are not continuous throughout the day and it is wise to administer the drugs only as necessary

The actual amount required varies widely according to the severity of the allergic symptoms to be controlled and the differences in individual susceptibility to toxic effects may require modifications or a change to a less toxic drug For children of 5 to 6 years about half the adult dose is advised For infants and smaller children the initial dosage should be reduced in proportion to body weight using the liquid preparations In the case of Pyribenzamine and Benadryl doses of *2 to 4 mg per pound of body weight per day are suitable*

Preparations

Tablets and Capsules for Children of 6 to 12 years

Ambodryl hydrochloride capsules 25 mg
Benadryl hydrochloride capsules 25 mg 50 mg
Chlor Trimeton 4 mg scored tablets 8 mg tablets for prolonged action
Co-Pyronil pulvules—Pyronil 15 mg Histadyl 25 mg and Clopane hydrochloride 12 5 mg
Decapryn succinate 12 5 and 25 mg scored tablets
Hydryllin tablets—diphenhydramine (Benadryl) 25 mg and aminophylline 100 mg
Neo-Antergan maleate 25 mg and 50 mg coated tablets
Perazil 50 mg scored tablets
Phenergan hydrochloride 12 5 mg tablets
Pyribenzamine hydrochloride 25 mg coated tablets 50 mg scored tablets
Tagathen 25 mg coated tablets
Teldrin spansules 8 mg 12 mg Chlorprophenpyridamine maleate (Chlor Trimeton) in a slowly adsorbed form
Thephorin tartrate 10 mg 25 mg tablets

Liquid Preparations for Infants and Young Children

Ambodryl hydrochloride elixir 12 5 mg in 5 ml
Benadryl hydrochloride elixir 12 5 mg in 5 ml
Chlor Trimeton syrup 2 5 mg in 5 ml
Phenergan hydrochloride syrup 6 25 mg in 5 ml
Pyribenzamine elixir 37 5 mg of Pyribenzamine citrate (equivalent to 25 mg of Pyribenzamine hydrochloride) in 5 ml
Thephorin tartrate syrup 10 mg in 5 ml

In general dosage of these liquid preparations is 0 5 to 1 ml per pound of body weight per day given in three or four doses

Sterile Solutions for Intramuscular Injections

Benadryl hydrochloride 10 mg per cc 10 cc vials
Pyribenzamine hydrochloride 25 mg per cc 1 cc ampules
Chlor Trimeton 10 mg per cc 1 cc ampule and 100 mg per cc 2 cc vials

Ointments and Creams

Benadryl hydrochloride cream 2 per cent in a water miscible base
Pyribenzamine ointment 2 per cent in petrolatum base
Pyribenzamine cream 2 per cent in water miscible base
Thephorin tartrate ointment 5 per cent in Carbowax base

ADRENERGIC DRUGS

The inhibiting influence of the sympathetic nervous system and the adrenal medullary hormones on many atopic and anaphylactic reactions has been discussed in Chapter 3

Epinephrine the principal hormone secreted by the medulla of the adrenal gland has the property of stimulating the mechanisms normally stimulated by the sympathetic nerves and correspondingly inhibits many of the manifestations of anaphylactic and atopic reactions Ephedrine a drug derived from plants and the synthetic drugs isopropylarterenol (Isuprel) Neo-Synephrine and Privine have related chemical structures and pharmacologic properties These adrenergic or sympathicommetic drugs are basically similar but vary in the speed intensity and duration of their actions and in the routes of administration by which they are most effective

Epinephrine

Epinephrine is the most rapidly effective and potent drug of the group but its period of action is relatively short and it is not effective when given by mouth Because of its prompt and potent action when injected intramuscularly it is one of the most useful drugs for the relief of acute asthma anaphylactic shock severe generalized atopic reactions due to ingested or injected allergens acute urticaria and angioedema The disadvantage of the brief action of its soluble form may be overcome to some extent by injection of a slowly adsorbed suspension in oil or of the relatively insoluble tannate (Sus Phrine) Relatively strong (1 100) solutions are effective for the relief of asthma when inhaled as aerosols from suitable nebulizers In combination with cocaine it is useful in eye drops for the relief of allergic conjunctivitis For nose drops ephedrine and Neo-Synephrine are more suitable

Epinephrine is a potent drug and its systemic use is likely to produce tachycardia palpitations excitement and pallor These side effects may be serious in children with heart disease but in the otherwise healthy child they are more unpleasant than dangerous When epinephrine is used in a nebulizer care must be taken to hold the nebulizer in such a position as to avoid swallowing drops of the solution as this causes severe epigastric pains which may easily be mistaken for acute abdominal disease

The dose of epinephrine required will vary greatly with the severity of the symptoms being treated Except in the most severe emergencies it is wise to use a relatively small dose (0 1 to 0 3 ml) initially and repeat every 10 minutes for two or three doses until the desired therapeutic effect is obtained

Preparations and Prescriptions —Epinephrine hydrochloride (Adrenalin hydrochloride) 1 1 000 sterile solution for subcutaneous or intramuscular injection Supplied in 1 ml ampules and 30 ml rubber capped vials dosage 0 1 to 0 5 ml repeated every 10 to 20 minutes if necessary until relief is obtained or side effects become troublesome

Epinephrine in oil 1 500 for intramuscular injection is somewhat slower in action but effects persist for six to eight hours It may be used to supplement and sustain the effect of the aqueous solution Supplied in 1 ml ampules dosage 0 5 to 1 0 ml every 6 to 8 hours if necessary Sus Phrine an aqueous suspension of epinephrine tannate 1 200 serves the same purpose Dosage 0 1 to 0 3 ml every 4 to 6 hours if necessary

Epinephrine hydrochloride 1 100 solution for inhalation Supplied in 5 or 10 ml bottles to be used in a suitable nebulizer such as the De Vilbiss No 40 or the Vaponefrin Dosage cannot be determined exactly two to four inhalations should be given and repeated as necessary Excessive use causes dryness and irritation of the throat This may be minimized by gargling with water after each use but if the nebulizer is being used more than 4 or 5 times a day it is well to supplement its use with an oral medication of longer action Vaponefrin solution is a proprietary medication serving the same purpose

Epinephrine and Cocaine Eye Drops

Cocaine hydrochloride		0 1 Gm
Boric acid		1 0 Gm
Epinephrine hydrochloride 1 1 000		8 ml
Rose water	to	30 ml
Sig 1 or 2 drops in each eye as necessary		

This combination is useful for the ocular symptoms of hay fever for controlling the conjunctival irritation of general atopic reactions and for stopping excessive reactions to conjunctival tests

Ephedrine

Ephedrine is slower in action and less potent than epinephrine but its action is more prolonged (four to six hours) and it is effective when given by the oral route It tends to produce central stimulation and therefore is often used in combination with a mild sedative Alone or in combination with a sedative it is effective in the control of mild or moderate asthma and urticaria In general the antihistamines are more useful for the treatment of allergic rhinitis The efficacy in asthma is potentiated by combination with theophylline The 1 per cent solution is used in nose drops but care must be taken to avoid prolonged and excessive use

Preparations and Prescriptions —Ephedrine hydrochloride or sulfate 25 mg tablets or capsules For children of 6 years or older one every 4 to 6 hours as necessary

Ephedrine hydrochloride 3 per cent aqueous solution For fractional doses in infants 5 to 15 drops every 4 hours if necessary

Ephedrine and Amytal capsules Ephedrine sulfate 25 mg and amobarbital 50 mg For children of 6 years or older one every 4 hours if necessary

Ephedrine hydrochloride 1 per cent in saline is used as a vasoconstricting nose drop Use should be limited to a few days if possible to avoid secondary irritation

Isopropylarterenol

This drug marketed as Isuprel and Norisodrine has an effect similar to that of epinephrine in the relief of asthma It also stimulates myocardial action and may cause palpitation but does not raise blood pressure It is used chiefly by inhalation Isuprel as a solution in a nebulizer such as those used for epinephrine and Norisodrine in a powdered form from a special inhaler supplied by the manufacturer Isuprel is also supplied in tablets for sublingual use

Preparations -Isuprel hydrochloride 1 100 and 1 200 solutions for inhalation are used for inhalation in the same way as epinephrine 1 100 and are essentially comparable in potency

Isuprel hydrochloride sublingual tablets 10 mg ½ to 1 tablet under tongue three to four times a day if necessary

Norisodrine sulfate 10 per cent and 25 per cent powder This is inhaled from a special plastic inhaler (Aerohalor) Suitable only for older children who should be carefully instructed in use to avoid overdosage The 10 per cent powder should always be used first

Phenylephrine Hydrochloride (Neo-Synephrine) and Naphazoline Hydrochloride (Privine)

These drugs are of little value in the treatment of asthma and urticaria but highly effective as vasoconstricting nose drops In both infective and allergic rhinitis they produce prompt shrinkage of the congested mucosa Unfortunately use continued over a period of more than two or three days tends to cause irritation of the membrane or rebound congestion as the initial effects wear off This secondary congestion is most likely to occur with the use of Privine but may be produced by any drugs of the group Since the symptoms of this secondary congestion are essentially similar to those for which the nose drops were first used the tendency of those not familiar with the danger is to use them more and more frequently setting up a vicious circle of medication and irritation which may persist indefinitely The sensitive nasal mucosa of the patient with allergic rhinitis is particularly susceptible to this irritation Therefore vasoconstricting nose drops are not useful for the treatment of chronic allergic rhinitis They may be beneficial for the relief of acute colds and sinusitis but their use should be limited to a few days at a time The mildest preparations such as Neo Synephrine ¼ per cent are preferable

Preparations —Neo-Synephrine ¼ per cent solution Nose drops one or two drops in each nostril every 4 hours if necessary

Privine 0 05 per cent in isotonic salt solution One or two drops in each nostril every 4 hours if necessary Caution Not to be used for more than three successive days

CORTISONE AND RELATED COMPOUNDS

As previously indicated (Chapter 3) the adrenal cortical hormones strongly inhibit many types of allergic reactions including serum sickness essentially all of the atopic diseases contact dermatitis and many of the more severe drug allergies These actions are of great value in producing temporary symptomatic relief of severe allergic disease The hormones are among the most effective therapeutic agents in many of these conditions but the effects are always palliative rather than curative Except in conditions which are naturally of limited duration such as serum sickness and drug reactions recurrences of symptoms may be expected when the treatment is discontinued In chronic allergic disease they are rarely satisfactory as the main treatment over a period of time but are very useful for alleviation of acute exacerbation of symptoms

The effects may be obtained by the administration of *cortisone* or *hydrocortisone* hormones naturally secreted by the adrenal cortex or the synthetic derivatives *prednisone* and *prednisolone* In children with normally functioning adrenal cortices (which includes practically all allergic children) similar results may be obtained by the use of *corticotropin* the pituitary adrenocorticotropic hormone which stimulates the secretion of cortisone and hydrocortisone by the adrenal glands of the patient

The natural hormones have many varied effects on the body which must be kept in mind when they are used as systemic medications for more than a week or two Among the most important is their effects on salt and water metabolism Large doses cause retention of sodium and water and loss of potassium salts This may be manifested by rapid gain of weight and dependent edema In children with heart disease congestive failure may be precipitated To avoid these complications children receiving cortisone or hydrocortisone for more than a week should be on a salt free diet and be given potassium chloride one Gm daily Glucose metabolism is also often affected with transitory glycosuria and increase of the blood sugar making the regulation of pre existing diabetes mellitus more difficult Appetite is increased and prolonged use may lead to obesity which characteristically affects the upper part of the trunk and the face to produce moon face There is a tendency to growth of hair on the face and acne is a frequent complication

These drugs may cause exaltation mental confusion and even acute psychosis which subsides within a few days when treatment is discontinued They also have an unfavorable effect on pre existing peptic ulcer increasing the tendency to hemorrhage and perforation

The effects of these drugs on infection is also unfavorable Latent or healed tuberculosis may become active during their use and acute infections tend to run a more severe course When infection occurs during treatment with cortisone it is wise to give suitable antibiotics promptly and in adequate doses The danger is particularly great in the case of chicken pox which is not amenable to treatment with antibiotics This disease usually mild may be serious and occasionally fatal when a child is being treated with cortisone While a child is receiving drugs of this group great care is essential to avoid exposure to chicken

pox If a child who has not previously had the disease is known to be exposed the drug should be stopped during the incubation period If chicken pox de velops while the drug is being given its use should be stopped as abruptly as is considered safe

Since the usual therapeutic doses of cortisone and hydrocortisone are in excess of the normal requirements of the body the adrenal cortex remains inactive while they are given After a period of several weeks it may undergo atrophy by disuse This produces a temporary state of adrenal cortical insufficiency which is not apparent as long as the exogenous hormone is given but may be serious if its use is stopped abruptly in a period of physical stress due to acute infection trauma or major surgery The occurrence of any such emergency in a child who has been receiving cortical hormones for several weeks calls for continua tion or increased dosage rather than abrupt stopping of the drug Whenever drugs of this group have been given over a period of more than two weeks abrupt discontinuation is hazardous The dose should be gradually tapered off over a period of one to four weeks depending on the size of the dose and duration of treatment

Corticotropin may produce any of the side effects produced by cortisone it does not cause disuse atrophy of the adrenal cortex but may produce atrophy of the secretory cells of the anterior pituitary with the same clinical results

Because of the untoward effects of prolonged use the administration of cortical hormones for allergic disease is best limited to brief periods of unusually severe symptoms and conditions naturally of short duration When relatively small doses are used for periods of one or two weeks the incidence of undesir able side effects is negligible

Prednisone and prednisolone synthetic modifications of the natural hor mones cortisone and hydrocortisone are more potent in their therapeutic ef fects and have far less influence on salt and water retention Most of their other side effects are essentially similar to those of the natural hormones An other synthetic modification fluorohydrocortisone is not suitable for systemic treatment of allergic disease but is highly effective for local application to allergic skin lesions

For systemic use all of the cortisone derivatives are effective when given by mouth Corticotropin on the other hand must be administered parenterally The aqueous solution is effective for only about six hours when injected intra muscularly but the slowly adsorbed gel form acts over a period of twenty four hours or more and is therefore generally used in allergy For more rapid action in severe allergic states the soluble form may be diluted with 500 ml of dextrose solution and given intravenously by slow drip

Hydrocortisone and fluorohydrocortisone in ointment bases are useful as *topical applications for contact dermatitis* infantile eczema and atopic derma titis They are also available in nose drops but the effectiveness of these prepara tions is questionable Cortisone is effective for topical use in the eye

Oral Preparations —Cortisone acetate 25 mg hydrocortisone 20 mg predni sone[1] 5 mg and prednisolone 5 mg are essentially equal tablet for tablet in therapeutic effects Dosage varies widely depending on the severity of the condition being treated The initial dosage should be adequate to produce re lief in two or three days after which it may be gradually reduced over a period of three or four more days For older children with severe allergies the initial dosage may be 1 or 2 of the above mentioned tablets every 6 hours Infants and young children require about half this amount If it is necessary to continue treatment over a period of several weeks the dose should be reduced to the minimum which will control the symptoms

Injectable Preparations —*Corticotropin gel* (40 or 80 units per ml in 5 ml vials) dosage of 20 to 40 units intramuscularly is occasionally useful to start treat ment It may be injected daily for two or three days but once an effect is estab lished the oral steroid preparations are generally preferable

Corticotropin powder in vials of 10 25 or 40 U S P units 10 to 15 units diluted in 500 ml of isotonic dextrose solution may be given intravenously by slow drip over a period of 6 to 8 hours when rapid action is desired in acutely ill children

Preparations for Topical Use —*Hydrocortisone ointment* ½ and 1 per cent and *fluorohydrocortisone ointment* ¼ *per cent are effective topical applications to* skin lesions When used for rashes which have been secondarily infected by scratching they may be combined with an antibiotic such as neomycin or Ter ramycin These combinations are available in the proprietary preparations Neo Cortef and Terra Cortril

Ophthalmic suspension of cortisone acetate 0 5 per cent and 2 5 per cent in 5 ml vials and *ophthalmic ointment of cortisone acetate* 1 5 per cent in ⅛ oz tubes are suitable for topical treatment of the conjunctivae The ointment is also available with bacitracin

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M t o t n
Met o tel e Stera

Chapter 5

ANAPHYLAXIS IN PEDIATRIC PRACTICE

Definition.—As indicated in the discussion of terminology in Chapter 1 the term anaphylaxis is here used to denote the type of sensitization which results from the presence of antigen within the tissues and is manifested by an immediate reaction to subsequent parenteral contact with the antigen The association of such sensitization in experimental animals with circulating precipitin complement fixing and anaphylactic antibodies has been described in Chapter 2 The anaphylactic sensitization of the human child is similar in the manner of development and the manifestations of reaction In a typical case of anaphylactic sensitization induced by a therapeutic injection of heterologous antiserum the plasma of the child shows the same types of antibody activity as does the experimental animal and also the skin sensitizing antibody which may or may not be demonstrable in the experimental animal In other instances of human anaphylactic sensitization one or more of these forms of antibody activity may be lacking Anaphylactic sensitization is distinguished from atopy by the method of developing allergy by the less apparent influence of hereditary factors and by the types of associated circulating antibodies

Etiology

Anaphylactic sensitization of children is most often due to previous administration of heterologous antisera less often to other biologic medications which contain foreign protein or to nonprotein drugs such as penicillin Aside from therapeutic agents it may be due to stings or bites of insects or to the presence of metazoan parasites in the tissues A mild and clinically insignificant anaphylactic type of sensitization to the type specific carbohydrate of the pneumococcus may also be demonstrated during recovery from pneumonia These

varied causes indicate that the presence of foreign antigen in the tissues can readily produce sensitization of this type Heredity is not an important factor

ANAPHYLACTIC SHOCK

The most typical manifestation of anaphylactic sensitization is acute shock produced by injection of antigen into the tissues or blood stream The nature symptoms and treatment of anaphylactic shock are the same whether it is caused by the injection of heterologous antiserum or of penicillin by the sting of a bee or by rupture of a hydatid cyst within the body

Physiology

Because of its explosive nature and unexpected occurrence and the need for immediate treatment anaphylactic shock in the human child offers little opportunity for physiologic studies beyond the simple observation of symptoms The principal features are dilatation and increased permeability of the small blood vessels spasm of smooth muscle particularly of the bronchioles and fall of blood pressure On the basis of extensive experimental studies on lower animals cited in Chapter 2 it appears probable that these reactions are largely due to the release of histamine in the tissues It is possible that other physiologically active intermediary substances may play a part but direct evidence of their nature and action is not available

It may also be noted that the urticarial wheal produced in the anaphylactically sensitized child by a skin test with the specific antigen is similar to that produced by histamine

Anaphylactic shock is very similar in its manifestations to the general allergic reaction produced by the injection of an excessive dose of antigen into an atopically sensitive person Presumably this reflects the fact that both are mediated by the liberation of histamine

Symptoms

Although anaphylactic shock undoubtedly involves many organs of the body the most obvious features are those of the skin the respiratory system and the circulation The skin manifestations include flushing itching or burning of the skin particularly the face and upper chest urticaria which may become confluent over large areas and angioedema particularly of the face tongue and hands The respiratory symptoms may be tightness or pain in the anterior chest irritative cough wheezing and intense dyspnea with cyanosis Circulatory failure is manifested by a marked drop of blood pressure imperceptible pulse pallor vertigo syncope and coma

The prominence of these different manifestations varies with the severity of the reaction In the most rapidly progressive reactions circulatory failure is apparent within a few minutes after the injection of antigen and death may occur within ten minutes In such cases the skin manifestations rarely develop and respiratory difficulties are not prominent In less acute shock the skin

manifestations often appear first and are followed by respiratory difficulties and falling blood pressure the initial flush of the face giving way to cyanosis or pallor

Diagnosis

The dramatic sequence of cause and effect usually leaves little doubt as to the diagnosis of anaphylactic shock In those cases where immediate circulatory collapse occurs without the more characteristic allergic skin and respiratory manifestations severe shock may be confused at first with simple fainting due to the needle puncture

The diagnosis of *anaphylactic sensitization* before shock occurs is of paramount importance so that injections of the specific antigen will not be given In general the intracutaneous tests with protein antigens in suitable dilutions are valid evidence In anaphylactic sensitization to nonprotein drugs reactions to skin tests are less reliable Practical details are given in subsequent discussions of the various types of antigens

Treatment

The treatment of anaphylactic shock must be prompt and vigorous When ever antisera or other substances commonly causing shock are injected epinephrine 1 1 000 solution and a rubber tourniquet should be at hand When possible injections should be given into the arm or thigh at a point permitting effective use of the tourniquet if necessary

At the first symptoms of shock the tourniquet should be applied if possible and epinephrine 0 2 to 0 5 ml injected intramuscularly Subsequent doses of epinephrine should be given every 5 to 10 minutes until an effect is obtained After one or two doses of epinephrine an antihistamine such as Chlor Trimeton 10 mg or Benadryl 20 mg may be injected intramuscularly for supplementary effect but one should not rely upon antihistamines to replace the more rapidly acting epinephrine For circulatory failure nikethamide (Coramine) 1 ml may be injected followed by levarterenol (Levophed) by infusion if hypotension persists Dyspnea and cyanosis should be treated by inhalation of oxygen Hydrocortisone by infusion has been recommended for anaphylactic shock but the *limited experience with its use does not warrant substituting it for the better* known drugs

ALLERGIC REACTIONS TO INSECT STINGS AND BITES

The bee and other stinging insects inject into the skin venom which is both toxic and a potential cause of anaphylactic sensitization Many simultaneous stings may cause a type of shock and occasionally death of small children who are not sensitized purely through toxic effects The systemic reactions to one or two stings are due to anaphylactic sensitization acquired through previous stings

Etiology

The principal stinging insects of the United States are the honeybee the wasp the yellow jacket and the hornet Some knowledge of the various insects may be *helpful in attempting to identify the species involved* Yellow jackets nest in the ground wild bees usually in hollow trees wasps and hornets make mud or papery nests in elevated locations often under the eaves of buildings The honeybee usually leaves his stinger in the wound and subsequently dies of injury to its abdomen The yellow jacket wasp and hornet can sting repeatedly

Information on the nature and specificity of the antigens in the venom is scanty The antigen can be extracted from the body of the insect and preparations for testing and treatment are commercially available Biologically wasps yellow jackets and hornets are related while honeybees belong to a different family However the possibility of cross reactions cannot be excluded Identification of the stinging insect is often impossible so that it is difficult to be sure if previous stings have been by the same type of insect

Symptoms

The usual history is one of increasingly severe reactions as the child receives repeated stings over a period of months or years Excessive local swellings may be followed by general urticaria and then typical anaphylactic shock which is occasionally fatal

Treatment

The treatment of the acute reaction is that previously described for anaphylactic shock in general

The rapidity of the reaction and the fact that stings are *usually* incurred in suburban or rural areas make it essential that the family of any child who has once had such a reaction be prepared to give emergency treatment without awaiting the arrival of a doctor They should be equipped with a rubber tourniquet a syringe which is kept sterile in a suitable container epinephrine 1 1 000 and an injectible antihistamine and should be carefully instructed in their use In the case of a severe reaction application of the tourniquet and the first injection of epinephrine should precede taking time to call a physician

The importance of avoiding subsequent stings is self-evident Nests in the *vicinity of the house should* be destroyed at night when the insects are quiescent by spraying heavily with an aerosol bomb In the case of yellow jacket nests in the ground burning out with kerosene may be considered

Immunization is advisable in all children who have suffered severe general reactions but should not be relied upon to the degree of neglecting the preparations for emergency treatment *This is preceded by intracutaneous skin tests* to determine the degree of sensitization Unless the offending insect has been definitely identified tests should be done with bee wasp and yellow jacket The initial test should be done with 0 02 ml of an extract containing 1 protein nitrogen unit per milliliter or the equivalent If this gives little or no reaction

subsequent tests are done with successive tenfold increases in concentration until a definite reaction is obtained If the reaction and the history indicate specific sensitization to one of the three types of insects only this one need be used in treatment When reactions to two or three are noted it is wise to treat with a mixture of these antigens

Injection treatment is started with 0 1 ml of the next weaker dilution to that which gives a definite skin reaction Subsequent doses are given once or twice a week in accordance with the principles set forth in Chapter 10 The optimal top dose is not easily decided Approximately 1 000 protein nitrogen units may be considered suitable unless excessive local reactions prevent reaching this level

Even after injection treatment any sting should be treated promptly with epinephrine and the use of a tourniquet if its location permits

Prognosis

The reaction to a sting is usually rapid and of relatively brief duration Once a general reaction has occurred sensitization may be expected to persist for years Unless adequate treatment is given the expectation is that each sting may produce a more severe reaction than the previous one

Biting Insects

A great variety of insects and related arthropods (ectoparasites) bite human beings in order to feed on the blood Among these are mosquitoes gnats ticks bedbugs fleas lice and various flies The sucking of blood is facilitated by the injection into the skin of saliva which prevents its clotting This injection of saliva is of great medical importance in the transmission of many infectious diseases It also may induce an allergic reaction in the person who is bitten

In the nonsensitive child the bites of mosquitoes and flies cause only transitory itching or slight pain and leave small papules often with a visible puncture mark which disappear in a day or two The sensitized child reacts with a larger urticarial lesion with intense itching which may last twenty four hours or more The early urticarial reaction may progress to a papulovesicular lesion which persists for several days Bites about the face may cause angioedema of the eyelids ears or lips Multiple bites may cause general malaise but rarely if ever actual symptoms of anaphylactic shock As noted in Chapter 14 *papular urticaria* of children appears to be due in most cases to allergic reactions to bed bugs or other arthropods

The allergic nature of these reactions has frequently been established by skin tests with extracts of the appropriate insects but such tests are rarely necessary for purposes of diagnosis

The principal point in the treatment is avoidance of contact by methods appropriate to the particular type of insect such as screening use of insecticides and repellants etc

Relief of urticarial lesions and reduction of edema is generally afforded by oral use of antihistamine drugs Topical application of these drugs is also helpful in the relief of itching Desensitization is rarely necessary

SENSITIZATION TO PARASITIC WORMS

The presence of parasitic worms in the tissues affords ample opportunity for the development of anaphylactic sensitization Since the source of antigen the worms is present in the tissues at the time of antibody formation the allergic manifestations tend to be prolonged and mild without the abrupt character of anaphylactic shock

Etiology

Any of the parasitic worms may cause sensitization The allergic phenomena are more marked in the infestations by parasites which in their life cycle actually invade the tissues than in the case of those which never leave the gastrointestinal tract Among the former are Ascaris Toxocara the ascaroid worm of dogs and cats Schistosoma Trichinella and Echinococcus

Diagnostic Skin and Serologic Tests

The development of allergy to the worms is associated with the presence of the circulating antibodies typical of anaphylaxis Precipitins and complement fixation are demonstrable in schistosomiasis trichinosis echinococcus (hydatid) disease and filariasis Skin tests with antigens derived from these worms and also ascaris give typical immediate wheal reaction in the infested child These tests also occasionally show a delayed type of reaction after 24 to 48 hours the diagnostic significance of which is questionable

The skin tests with Trichinella and Echinococcus antigens are of practical value in diagnosis of these infestations although they give some cross reactions in patients infested with other worms The complement fixation tests are also of diagnostic value although the Trichinella test gives false positive reactions in some cases of periarteritis nodosa In general both skin and serologic tests become positive about the third week of infestation Skin tests and complement fixation have also been utilized in the diagnosis of schistosomiasis and filariasis Unfortunately except for the Trichinella antigen for intracutaneous test * these antigens are not commercially available

Allergic Manifestations

The most frequent allergic manifestation of the presence of these parasites is urticaria which is particularly likely to occur during the early stages of infestation but after the development of antibodies Allergic reactions of the lung to parasites are discussed in the following section In hydatid disease after the Echinococcus becomes encysted relatively little antigen is absorbed but a high degree of sensitization remains In this stage rupture of the cyst by trauma

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Supplied by Lederle Laboratories

causes a sudden release of antigenic fluid most often into the peritoneal cavity This abrupt exposure causes typical anaphylactic shock often severe or even fatal

The intense eosinophilia (15 to 50 per cent) which accompanies most infestations by parasitic worms is also an evidence of the allergic reaction

LOEFFLER S SYNDROME

In 1932 Loeffler described the combination of transitory pulmonary infiltrations with marked eosinophilia of the peripheral blood which is commonly designated as *Loeffler s syndrome* The symptoms noted in his cases were variable and usually relatively mild with spontaneous recovery generally occurring in a few weeks Weingarten in 1933, reported the same pulmonary and blood findings in cases of *tropical eosinophilia* which was common in India The illness of Weingarten s patients was generally more severe and persistent than in those described by Loeffler and recovery seemed to depend on treatment with arsenicals Because of their clinical similarity and the absence of proof of etiology in most cases many writers on the subject have considered the two conditions the same Others have applied the terms *eosinophilic pneumonopathy* and *allergic pneumonia* to the same clinical pictures

These terms are used interchangeably to designate a rather poorly defined group of diseases having in common the two features of marked eosinophilia and a succession of transitory infiltrations of the lungs apparent on serial x rays of the chest It is quite probable that the etiology of the illness may vary in different patients presenting this picture

The infiltrations in the lung tissue are believed to manifest an allergic reaction of the interstitial tissue of that organ In some cases they are associated with infestation by parasitic worms and apparently result from allergic inflammation due to the presence of larvae in the lung In other cases radiographically similar infiltrations are associated with a generalized allergic reaction of the blood vessels and the connective tissue of the viscera which is a manifestation of periarteritis nodosa The causative allergen in such instances is rarely determined Some cases in adults have been attributed to drug allergy Some authors have attributed allergic lung infiltrations in patients with bronchial asthma to inhaled allergens This etiology seems doubtful unless in rare cases of inhalation of a massive dose of antigen Actual proof of the relationship is impossible

It is obvious that such a varied group of cases cannot be considered a disease entity The course and prognosis will depend greatly on the etiology of the particular case and the presence of associated disease such as periarteritis nodosa The discussion which follows refers only to Loeffler s syndrome occurring in association with parasitic infestation or in children without evidence of serious complicating disease

Etiology

In a large proportion of the patients with Loeffler s syndrome no specific etiology is demonstrated In those instances where a definite cause is established

by far the most common is infestation with parasitic worms The worm most often implicated is Ascaris less frequently Schistosoma or Toxocara the ascaroid worm infesting dogs and cats The larvae of all of these parasites migrate through the lungs in the early stages of infestation Both Ascaris and Toxocara are widely distributed throughout the world Schistosomiasis is acquired only in tropical countries where the types of snails which act as intermediate hosts are found such as in *the West Indies and the northern parts of South America*

Proof of the presence of these worms in patients with Loeffler s syndrome is not easy The only readily available method of establishing the diagnosis of infestation is by demonstration of ova or parasites in the feces which depends on the presence of adult worms in the gastrointestinal system When infestation with Ascaris is acquired the larvae are present in the lung within a week or two while the appearance of ova in the stool occurs only after two or three months The presence of ova in the stools during Loeffler s syndrome depends upon *repeated infection with the parasites in different stages of development In children* living under conditions conducive to exposure such reinfection is very common The development of Toxocara in the body follows a similar cycle *but in many cases the larvae become encysted in the tissues and fail to reach the* adult form so that ova never appear

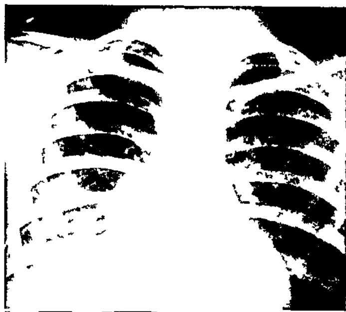
Despite the lack of adequate methods of detecting the presence of larvae in the lung many writers have considered parasites to be the main cause of Loeffler s syndrome *Support for this view is offered by Scheer s review of 35* children with proved ascariasis In this group he found three cases with definite Loeffler s syndrome and three others with suggestive features In view of the relative rarity of Loeffler s syndrome these figures are highly suggestive of an etiologic relationship More direct evidence is offered by Loeffler s observations on volunteers (adult) who swallowed ascaris larvae After six days infiltrations of the lung were detected by x ray and after eight days these were well developed Eosinophilia of the blood was apparent by the tenth day These studies leave little doubt that this clinical syndrome can be caused by ascaris infestation In the opinion of Loeffler ascaris is the most frequent cause

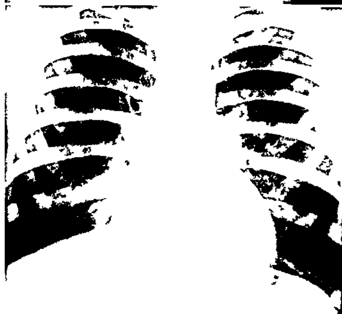
The allergic nature of the pulmonary infiltrations is suggested by their *evanescent character the pronounced eosinophilia* of the peripheral blood the presence of eosinophils in the sputum and frequently by mild asthma The syndrome is far more common in children with a personal or family history of atopic diseases but may occur in the absence of any evidence of this tendency

Symptoms

In general the symptoms are relatively mild and the general health little *affected even in patients whose chest x rays show* large areas of pulmonary infiltration Low grade fever may or may not be noted but there is little malaise Cough is commonly present but not severe and there may be an asthmatic type of bronchitis Sputum is usually absent when present it may show a predominance of eosinophils Auscultation of the chest reveals only a few rales or an absence of abnormal signs

A





B

Fig 1—Loeffler's syndrome in 11 year old Puerto Rican boy with schistosomiasis and hookworm. White blood count 13 000 with 51 per cent eosinophils. *A* Infiltration in right lower lung field. *B* Marked clearing after four days without specific treatment.

children with an atopic background but with large doses such as those formerly used in the treatment of pneumonia 80 to 90 per cent of patients developed symptoms The amount of serum injected is an important factor in the incidence Cerlough suggested that the incidence after diphtheria antitoxin was proportional to the square root of the volume injected rising from 10 per cent after 4 ml to 70 per cent after 144 ml The type of serum is also a factor the incidence being higher after scarlet fever antitoxin than diphtheria antitoxin The incidence is considerably reduced by modern methods of preparation of antiserum both concentrating the antibody from the crude serum so that less protein is injected and subjecting the antitoxin to partial enzymatic digestion which lessens its antigenicity

Immunologic Mechanism

Heterologous sera in general are excellent antigens and injection of moderate amounts is followed by the formation of typical precipitating antibodies The foreign serum proteins are only slowly eliminated from the body so that a considerable proportion of the injected antigen is still present at the end of the incubation period of antibody formation This co existence of residual antigen and newly formed antibody causes the reaction of serum sickness If a single pure serum protein is injected its concentration in the circulating plasma falls gradually during the incubation period then abruptly disappears at the *time of antibody formation Measurable amounts of circulating antibody are* demonstrable within a day after the disappearance of antigen The symptoms occur at the time of this change Crude antisera contain a number of different proteins which stimulate the formation of separate antibodies with different incubation periods The prolonged or recurrent serum sickness which may follow injection of such sera is the summation of several separate reactions to different antigens During its course *both antigen and antibody may be de*tectible in the blood if the tests for them employ the whole foreign serum as antigen and an antiserum to it as antibody Comparison with the system in which a pure antigen is injected indicates that one is observing the persistence of certain antigens of the foreign serum after antibodies for other components have been formed rather than the simultaneous presence of any one antigen and its specific antibody

At the time of recovery from serum sickness the skin reacts to an intracutaneous test with the causative serum by an immediate wheal reaction The blood generally contains antibodies capable of precipitating the antigen and of inducing passive anaphylaxis in guinea pigs and the Prausnitz Kustner reaction in human skin These persist for a variable period of weeks or months

Symptoms

The severity and duration of serum sickness depends to a great degree on the amount and type of antiserum injected The use of large volumes of unrefined horse antiserum as in the old treatment of pneumonia produces severe and prolonged reactions in a great percentage of patients *On the other hand*

the prophylactic dose of refined tetanus antitoxin which is now the most commonly used antiserum causes only a small incidence of serum sickness and most of the cases are mild lasting only three or four days

The incubation period is usually 6 to 12 days but may last as long as three weeks The first symptom is generalized swelling of the lymph nodes If the serum has been injected intramuscularly the swelling is often most marked in the nodes draining the site of injection The nodes may reach a diameter of 1 to 2 cm or more and are slightly tender to pressure In some cases the spleen is palpable This swelling of lymphoid tissue presumably reflects the reaction of antigen with antibodies at the side of their formation An elevation of temperature is almost uniformly present but may vary in severity from 100 F to 104 F and in duration from a day to a week Its course is usually irregularly spiking Edema of the face and occasionally of the dependent parts is a common symptom This may be reflected by a gain of 2 to 3 pounds in body weight and a decreased output of urine

Skin rashes are the most characteristic feature and no doubt many physicians hesitate to make the diagnosis in their absence However Kojis reported 48 cases (approximately 3 per cent of his series) in which the other symptoms were typical but no rash occurred By far the most frequent type of eruption is urticarial (approximately 90 per cent) but the rash may be simple erythema morbilliform purpuric or erythema multiforme The nature of the rash may change during the course of the illness If the serum has been injected subcutaneously or intramuscularly the rash usually appears first at the site of injection and becomes generalized Itching is a prominent feature of the usual urticarial rash but less marked with other forms

Pain and stiffness of the joints occur in approximately 50 per cent of children with serum sickness usually starting during the skin rash and persisting for a period of two to seven days In severe cases the joints may be definitely swollen tender and hot with periarticular edema and effusion into the synovial spaces The arthralgia occasionally involves the temporomandibular joints and may cause an erroneous suspicion of tetanus

Peripheral neuritis particularly involving the brachial plexus and often causing temporary paralysis is one of the less frequent manifestations of serum sickness usually occurring late in the disease Transitory cerebral symptoms of drowsiness headache and meningismus often follow the treatment of meningitis with intrathecal injections of antiserum and are occasionally seen in severe serum sickness after administration by other routes

The blood count often shows a leukopenia with decrease of granulocytes Von Pirquet and Schick considered this a prime evidence of serum sickness and reported one case in which the total white count fell to 880 However in the milder and atypical cases the occurrence of leukopenia is not sufficiently constant to be of great diagnostic value The eosinophil count shows no consistent change The sedimentation rate is usually moderately elevated The urine may contain albumin and casts in severe serum sickness

Pathology

Since serum sickness is rarely fatal and the lesions are relatively transitory knowledge of its pathologic manifestations is based on a few autopsy reports on adults The most striking change is necrotizing arteritis and periarteritis of the small arteries *including the coronary system* The endocardium may show lesions of both the valvular and mural portions which suggest rheumatic changes and the myocardium shows infiltration of wandering cells and proliferation of connective tissue Despite the histologic changes noted in the heart clinical evidence of carditis during serum sickness is rare Electrocardiographic changes have been reported *but are not distinctive*

Diagnosis

The diagnosis of serum sickness is rarely difficult if the physician is aware that an injection of foreign serum has been given The incubation period in most cases is 6 to 12 days and the occurrence of fever with lymphadenopathy after this interval is highly suggestive even in the absence of a characteristic rash If the history is unknown the symptoms may be suggestive of infectious mononucleosis measles or rheumatic fever

Greater difficulty may result when antiserum and penicillin are given *simultaneously since the entire picture of serum sickness with the same incu*bation period may develop as a delayed reaction to penicillin In this situation only the skin test and immunologic tests for circulating antibody are helpful in determining which antigen is responsible At the height of true serum sickness the intracutaneous skin test with the antiserum injected or normal serum of the same species is almost always positive This should be tested first in a dilution of 1 100 followed by 1 10 if necessary On the other hand if the reaction is due to penicillin the skin test with soluble penicillin is rarely positive *Thus* negative reactions with both antigens *strongly suggest a penicillin* reaction but does not entirely exclude serum sickness particularly if the symptoms are relatively mild While the same treatment is applicable to either type of reaction the differentiation is important in case future use of either agent is indicated

Treatment

In severe serum sickness the only satisfactory treatment is with cortisone its derivatives or corticotropin These agents usually control all the symptoms and since the disease is of limited duration they need be given only for a week *or so Cortisone 75 to 150 mg hydrocortisone* 60 to 120 mg or prednisone 20 to 40 mg daily in divided doses or corticotropin gel 20 to 40 units daily may be given for 3 or 4 days If the symptoms are then relieved the doses may be rapidly decreased and the drug stopped at the end of 7 or 8 days

In mild cases drugs applicable to the relief of individual symptoms may be adequate Antihistamine drugs lessen itching and at least partially suppress the urticarial rashes The more sedative agents such as Phenergan and Benadryl are desirable Local applications such as calamine lotion with phenol or

starch baths are also helpful for itching Ephedrine 10 to 25 mg by mouth or epinephrine 1 1 000 0 1 to 0 3 ml subcutaneously are also applicable to relief of urticaria Fever and joint pains may be treated with aspirin 0 15 to 0 6 Gm three or four times a day or codeine if necessary Restlessness not allayed by antihistamine drugs or aspirin may call for phenobarbital 8 to 15 mg every 3 hours

Prognosis

The danger to life is minimal As previously noted the duration of symptoms varies with the amount and type of antiserum but rarely exceeds a week with the preparations now in common use It is important to remember that a child recovering from serum sickness is acutely allergic to the causative serum and that severe reactions may result from further use of serum from the same species of animal With the passage of months this sensitization usually decreases but rarely may persist for several years

IMMEDIATE REACTIONS TO HETEROLOGOUS SERUM

Severe and often fatal immediate reactions to injections of heterologous antiserum may occur in children anaphylactically sensitized by a previous injection of serum from the same species of animal and in atopic children naturally sensitive to proteins of the animal species While the former is classed as anaphylactic and the latter as atopic the manifestations are essentially the same presumably because both are mediated by liberation of histamine in the body

Immunology

Any child who has previously received heterologous serum may have acquired anaphylactic sensitization The onset of sensitization is usually but not always manifested by serum sickness If serum sickness has occurred within two months the child will almost certainly be highly sensitive but neither the absence of clinical serum sickness nor the passage of several years since the injection enables one to disregard the possibility of sensitization Skin and eye tests with the serum are almost invariably positive if a significant degree of sensitization persists

The atopic children naturally sensitive to horse serum are in most cases affected by rhinitis or asthma on exposure to horse dander They usually show positive skin reactions to both the dander and the serum if tested in suitable dilutions suggesting that a common antigenic factor is present in both Many instances have been reported in which the skin reaction to horse serum was positive and that to horse dander negative but it is believed that such results are due to the use of very different doses of antigen in the two tests Horse serum diluted 1 10 which is generally used in skin tests preparatory to injecting antisera derived from horse contains over 100 000 protein nitrogen units per milliliter while the routine test solution of horse dander contains 100 units per milliliter Thus a minimal degree of sensitivity which is of no clinical importance in the production of symptoms on exposure to horse dander and not

detected by the usual tests with that antigen may be of importance when an injection of horse serum is given and be detectible by skin tests with the dilution of horse serum used for that purpose

Diagnosis of Serum Sensitization

Before heterologous antiserum is administered it is essential to question the patient and parents in regard to previous injections of antiserum and the occurrence of serum sickness or other reactions to them and also as to atopic symptoms particularly rhinitis or asthma related to exposure to horses and other animals

Regardless of the history a skin or conjunctival test must be performed The skin test is usually more easily interpreted by the average physician The material injected for the skin test may be a dilution of the antiserum or of normal serum of the same species Care is essential to avoid a dangerous reaction to the test itself or on the other hand failure to detect a significant degree of serum allergy Undiluted serum must not be used as serious reactions have resulted from injections of less than 0 1 ml into highly sensitive patients If the history of previous antiserum injection or atopic disease is clearly negative the initial test may be made with a 1 10 dilution Otherwise the 1 100 dilution is used and followed by the 1 10 if little or no reaction is noted For clear cut results the volume injected should not exceed 0 02 ml and the injection made sufficiently superficial to raise a distinct small bleb in the skin Fifteen to twenty minutes should be allowed before the final reading A marked reaction with pseudopods to the 1 100 dilution indicates a high degree of sensitization usually associated with atopic allergy to animal danders or recent serum sickness Even a slight reaction (4 to 5 mm wheal) to the 1 10 dilution requires caution in injecting the antiserum

The conjunctival test is performed by instilling a drop of serum into one conjunctival sac The concentration of serum is a 1 10 dilution for the first test in children with a positive history or undiluted serum for the final test A positive reaction is manifested by redness and itching of the conjunctiva after 15 to 20 minutes Excessive reactions may be stopped by instilling epinephrine 1 4 000 or epinephrine and cocaine eye drops (Chapter 4)

If carefully performed and observed over a period of 15 to 20 minutes these tests particularly the skin tests are reliable indices of the existence and a degree of sensitization However if there is a definite history of asthma or hay fever on contact with horses or of serum sickness within three months the patient should be treated as presumably sensitive even if the tests are negative

Administration of Antiserum to Sensitive Children

If the child reacts to horse serum an attempt should be made to secure antiserum prepared from another species of animal Tetanus antitoxin from cattle is generally available * but many of the less common antisera are made

* Produced by Sharp & Dohme

only from horses If antiserum of another species is obtained the same type of skin tests are done with dilutions of it before the injection is given

When serum to which the child is allergic must be used desensitization is necessary The possibility of densensitizing a serum sensitive child to a degree permitting the use of antiserum depends largely on whether the serum allergy is induced by a previous injection or spontaneously developed atopy With care and patience it is usually possible to desensitize the child with induced (anaphylactic) sensitization to a degree permitting intravenous injection of a considerable volume of serum This degree of desensitization is rarely possible in patients with spontaneous (atopic) sensitization but it may be possible to reach a tolerance permitting one to inject small amounts of serum subcutaneously or intramuscularly as in tetanus prophylaxis

The procedure of desensitization entails considerable risk of general reactions and must be carried out with adequate precautions to cope with such a possibility Epinephrine 1 1 000 solution an injectible antihistaminic such as Chlor Trimeton 100 mg /ml and a rubber tourniquet should be available The injections of serum should be given on the arm or thigh in a site permitting effective use of the tourniquet if a reaction should occur Administration of an oral antihistamine in twice the usual dose for the child s age or of epinephrine in oil 0 5 ml at the beginning of treatment will help to minimize reactions but does not lessen the need for other precautions

The general principle of desensitization is to begin with a dose based on the reaction to the skin test and to give injections every 20 to 30 minutes doubling the dose each time until the full amount of antiserum has been injected The actual schedule of doses will vary greatly with the degree of sensitization and the total dose of antiserum required If the skin test has produced a strong (three plus to four plus) reaction with pseudopods the first injection should not exceed twice the amount actually injected in the skin test If the reaction to the skin test is moderate (two plus) or slight (one plus) the first dose injected may be 20 to 50 times the amount used in the test The subsequent doses to complete the injection of a prophylactic dose of 1500 units of tetanus antitoxin the volume of which is approximately one milliliter are shown in Table III

If any injection of the series produces a large local reaction this dose should be repeated before progressing to the next Any systemic reaction is treated as described for anaphylactic shock in the previous chapter When the symptoms are controlled the desensitization is resumed if the patient s condition permits with the dose preceding the one which caused the reaction

When larger volumes of serum must be given intramuscularly or intravenously as in the treatment of tetanus the desensitization is started in the same way with subcutaneous injections When a dose of 1 ml of undiluted serum subcutaneously has been reached the serum may be given intramuscularly doubling the dose each time at intervals of 30 minutes If the intramuscular route is adequate for the therapeutic purpose of the antiserum use of the intravenous route is best avoided but in cases of dire need it has been used successfully After reaching a dose of 1 ml of the undiluted serum subcutaneously

0.1 ml diluted one hundredfold in saline is given very slowly intravenously. If this produces no untoward reaction, the serum is diluted fifty to one hundred fold in saline and allowed to drip into the vein at an initial rate of not more than 10 drops per minute *under constant observation*.

TABLE III

TYPICAL DESENSITIZING DOSES OF TETANUS ANTITOXIN IN CHILDREN OF MARKED AND MILD SENSITIVITY. DOSES GIVEN SUBCUTANEOUSLY AT INTERVALS OF 20 TO 30 MINUTES. TOTAL DOSE 1 ML.

DOSE NUMBER	SKIN REACTION FOUR PLUS TO TEST WITH 0.02 ML OF THE 1:100 DILUTION	SKIN REACTION TWO PLUS TO TEST WITH 0.02 ML OF THE 1:10 DILUTION
1	0.04 ml of 1:100	0.4 ml of 1:10
2	0.08 ml of 1:100	0.8 ml of 1:10
3	0.15 ml of 1:100	0.15 ml of undiluted
4	0.3 ml of 1:100	0.3 ml of undiluted
5	0.6 ml of 1:100	0.6 ml of undiluted
6	0.12 ml of 1:10	
7	0.25 ml of 1:10	
8	0.5 ml of 1:10	
9	0.1 ml of undiluted	
10	0.2 ml of undiluted	
11	0.4 ml of undiluted	
12	0.3 ml (remainder of total dose)	

Symptoms and Treatment of Immediate Shock Reactions

The manifestations of immediate serum reactions are essentially those of anaphylactic shock, regardless of whether the sensitization is of the anaphylactic type induced by a previous injection of serum or of the naturally acquired atopic type. The methods of treatment of anaphylactic shock outlined in Chapter 5 are equally applicable to both types.

ACCELERATED SERUM REACTIONS

Among patients who have had previous injections of the same heterologous antiserums, reactions to a subsequent injection not infrequently occur after an incubation period of one to five days, shorter than the typical incubation period of primary serum sickness but much longer than that of a typical immediate anaphylactic reaction. These reactions lack the shocking severity of immediate reactions but tend to be more acute than typical serum sickness. They are generally spoken of as accelerated reactions because of the early onset as compared to typical primary serum sickness. Accelerated reactions are most frequently observed among children who have received previous injections of serum 2 months to 2 years previously, but no exact time limits may be set. At the end of two or more months specific antibodies may no longer be detectible in the plasma. However, the antibody forming tissues retain a specific reactivity to the antigen, and a second injection of the same antigen, after circulating antibody has completely disappeared, causes a release of antibody far more rapidly and usually in higher concentration than the primary stimulating dose. This is the principle of the booster dose in various immunization procedures. If

the second injection of serum is given after the antibody level has fallen so low that there is no immediate reaction the rapid antibody response to the second injection produces symptoms of an accelerated reaction before the usual incubation period of serum sickness

Symptoms

After an incubation period of one to five days symptoms appear which resemble those of primary serum sickness These symptoms tend to be more acute and severe than those of typical serum sickness but the severity of both types of reactions varies so greatly that no clear distinction is possible except by the history and incubation period

Prevention and Treatment

If a second injection of antiserum of the same species must be given there is no effective method of preventing the occurrence of an accelerated reaction The skin test on patients susceptible to this type of reaction may be negative or mildly positive but the type of desensitization which helps to avoid imme diate reactions does not influence the occurrence of the accelerated reaction Prophylactic medication with antihistamine drugs ephedrine or aspirin started immediately after the second injection of serum may have some beneficial effect When the reaction has occurred the treatment is similar to that of serum sick ness of comparable severity

ARTHUS REACTIONS TO ANTISERA

The Arthus reaction is familiar as an experimental phenomenon in rab bits but is rarely seen in present day clinical medicine Similar reactions occa sionally progressing to local necrosis of tissues were observed in human patients during the earlier days of the use of antisera but with less common use of serum and better understanding of the principles of hypersensitivity they are now almost unknown The human being is not particularly susceptible to this type of reaction and the risk of a general anaphylactic reaction from the in advertent use of antiserum in a sensitized child is far greater than that of the Arthus type

Clinical Features

The Arthus reactions of human patients reported in the literature have almost invariably followed a series of injections of the same heterologous serum given at intervals of a few days to three weeks In most instances the successive injections caused increasing local reactions which became serious only after the fifth or sixth injection The more serious reactions usually followed in jections of serum which were given before the reaction to the previous injection had subsided Not infrequently the severe local reactions were accompanied by immediate general reactions

Prevention and Treatment

Recognition of the mode of production of such reaction should lead to avoidance in most cases In such diseases as tetanus where repeated injections of antiserum are needed daily intravenous injection is preferable to the intra muscular route

Once the Arthus reaction has developed treatment is symptomatic From animal experiments it appears that little may be expected from the use of anti histamine drugs or cortical hormones

USE OF TOXOIDS

From the longer viewpoint the most effective measure to prevent serum reactions of all types is active immunization The two types of antisera most commonly used at present are diphtheria and tetanus antitoxins The need for both of these can be avoided by proper immunization with toxoid which is highly effective in the prevention of both diseases if completed in advance of exposure One of the duties of the pediatrician is to see that these and other *immunizations are carried out on all children under his care In the case of* children allergic to animals or showing a positive skin reaction to horse serum the need is even greater When it is necessary to perform a series of skin tests on a child for diagnosis of allergic disease it is well to include horse serum routinely among them If the reaction is positive the parent should be warned not only of the possible danger of injecting heterologous antiserum but also of the advisability of adequate and maintained immunization with diphtheria and tetanus toxoids

Tetanus and diphtheria toxoids are culture filtrates containing foreign pro tein and they are themselves occasionally the cause of anaphylactic reactions although far less often than antitoxins Many of the reactions to tetanus toxoid noted soon after its use became common were shown to be related to peptones employed in the culture media With improved media and modern methods of purification such reactions are rare

The reactions reported usually follow immediately after the second dose sensitization having presumably resulted from the first dose given one or two months previously The manifestations are those of anaphylactic shock of vary ing degrees of severity Werne and Garrow reported the deaths of two identical twins ten months of age after their second injections of combined toxoid and pertussis vaccine The autopsy findings were those of anaphylactic shock and tests of the product injected showed it to be free of toxic properties

The incidence of such reactions is exceedingly low and the advantages of using toxoid far outweigh the risks involved However certain precautions are warranted to avoid the possibility of a severe reaction The existence of sensitization may be demonstrated in most instances by a skin test immediately before the second or subsequent injection A scratch test with undiluted toxoid or an intracutaneous test with 0.02 ml of a 1:10 dilution of the toxoid has been advised but has not been widely adopted as a routine procedure because of

the rarity of reactions In any case injections of toxoids should be given in a site on the arm which permits effective use of a tourniquet and the child kept under observation in the office for at least twenty minutes after the injection

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Chapter 7

THE ATOPIC DISEASES

CLINICAL ASSOCIATION OF DISEASES OF THE GROUP

Recognition of the frequent association of asthma and hay fever in the same patient antedates the concept of allergy Later it was recognized that patients with these diseases showed an unusual incidence of acute urticaria angioedema and gastrointestinal reactions to specific foods It was also apparent that infants who suffered from eczema were unusually susceptible to the later development of hay fever and asthma In those cases where the eczema persisted through childhood to adult life the incidence of respiratory allergies was particularly great It was evident that patients showing manifestations of allergy affecting one portion of the body were more susceptible to certain other types of allergic reaction affecting other organs A few patients with diseases of this group showed cerebral symptoms such as headache convulsions seizures or coma apparently related to allergy to foods Some authors believed there was a significant correlation between migraine and the allergic diseases but the evidence in this regard was less convincing and the difficulty of establishing migraine as a definite disease entity made real proof impossible On the other hand there was no apparent correlation between diseases of the asthma hay fever group and certain other diseases recognized as allergic such as contact dermatitis

Evidence was presented that the occurrence of these frequently associated allergic diseases was influenced by hereditary factors and furthermore that all diseases of the group were related to the same genetic factor so that one member of a family might show one disease of the group and another a different one The observation that most patients with each of these diseases showed

similar immediate urticarial reactions to skin tests with antigens gave further evidence of a close relationship

Recognizing that these apparently different diseases were manifestations of the same type of allergic reaction affecting different organs of the body Coca and Cooke applied the term atopy to the group

HEREDITY

Evidence of a Hereditary Factor—Many authors have published figures supporting the view that heredity is a strong factor in the tendency to develop allergic disease In the older medical literature dealing with hay fever and bronchial asthma there are reports that each is influenced by heredity A major study considering the two conditions together with certain obvious types of food allergy was made by Cooke and Vander Veer in 1916 They found that 48 per cent of 504 patients with such allergic diseases gave a history of the same or other diseases of the group among their antecedents while only 7 per cent of 204 normal persons studied as a control group gave such a history Among 26 families with a unilateral antecedent history 77 (51 per cent) of 150 children were affected and in 148 families with no antecedent history 205 (32 per cent) of 631 children were allergic

Numerous subsequent studies have reached similar conclusions Statistics assembled by Vaughan and Black from various sources indicate that 40 to 70 per cent of asthmatic children and 35 to 80 per cent of hay fever patients have a family history of allergy The reports of different authors are not strictly comparable in all cases since they have differed somewhat in the choice of the diseases included in the atopic group

Michael Schwartz avoided this arbitrary classification of diseases He approached the problem by studying groups of persons with and without bronchial asthma and observing the statistical evidence of genetic correlation of various different diseases to asthma He found that the occurrence of asthma was influenced by heredity and that vasomotor rhinitis atopic dermatitis and hay fever were genetically related to it The evidence with regard to urticaria and angioedema was less clear and there was no correlation with migraine epilepsy contact dermatitis psoriasis ichthyosis or gastrointestinal allergy Since the conclusion with regard to gastrointestinal allergy was based on relatively few cases and is at variance with general clinical experience its significance may well be questioned

Studies of homozygous (identical) twins have shown that the presence of atopic disease in one twin is generally accompanied by evidence of the same tendency in the other This tendency may be manifested by actual clinical symptoms or simply a latent tendency evidenced by urticarial skin reactions to skin tests with allergens often but not always the same ones to which the other twin reacts

The available evidence in conjunction with unpublished clinical impressions of many other workers in the field has lead to general acceptance of the view that heredity is an important factor in the occurrence of atopic disease

The published statistics are perhaps less conclusive than might be desired and have been criticized by Ratner and others

The weakest point in the studies is the relatively large number of atopic patients who have given no antecedent history However it is important to remember that many of the largest studies were made at a time when the concept of allergy was very new and attempts to determine the existence of allergic diseases in previous generations were obviously subject to error Furthermore as noted in regard to twins it is apparent that persons may carry the hereditary factor and transmit it to their progeny without showing obvious symptoms of allergic diseases The age of onset of atopic diseases varies from infancy to late middle age so that children may occasionally manifest these conditions before their parents do and if the parent dies at a young age of some other cause the hereditary source may never be obvious

Without collecting any significantly large group of statistics we have been impressed by the fact that among children of families where both parents are affected by overt atopic disease the incidence of such diseases is very high approximately 75 per cent

The scarcity of impressive new studies of the problem in recent years may no doubt be attributed to the fact that the importance of heredity is so generally accepted that further compilation of statistics is considered fruitless by most investigators It seems logical to accept the concept of heredity as an important predisposing factor in atopic disease although possibly not an essential factor since it is impossible to trace it genetically in every case From the standpoint of practical diagnosis a strong family history is certainly a valuable clue suggesting the possibility of atopic disease in a child

Heredity and Age of Onset—Cooke and Vander Veer and also Spain and Cooke found that the age of onset of symptoms depended in part on the hereditary background In families with a bilateral antecedent history of atopy a large proportion of children develop atopic disease in infancy or early childhood In families with a unilateral antecedent history the incidence of onset reached a peak about the time of puberty and in families with a negative history the age of onset was most often in adult life

Mendelian Analysis of Hereditary Factor—Attempts to analyze the heredity of atopic disease in terms of Mendelian genes have led to varying results as might be expected from the many possibilities of error Cooke and Vander Veer believed the allergic factor was a dominant character Adkinson a recessive Wiener Zieve and Fries concluded that it was a partial dominant the child with a double allergic factor almost certainly developing atopic symptoms before puberty the child with one allergic and one normal factor tending to develop symptoms after puberty but often carrying the trait without any overt symptoms and the person with double normal factors never showing symptoms

Distinction Between Heredity and Passive Sensitization—This genetic predisposition to atopy is obviously a different phenomenon from the passive sensitization of the young of an anaphylactically sensitized female guinea pig by antibodies transmitted through the placenta In the latter case the young are born with a transient passive sensitization to the same antigen as the mother

while sensitization of the male parent has no effect In human atopy specific sensitizing antibodies do not pass the placenta and the infant is not born passively sensitized In general neither allergy to a specific antigen nor a particular disease manifestation of atopy is inherited The child inherits equally from both parents a tendency to develop active atopic sensitization to antigens with which he comes into contact Since the incidence of certain symptoms such as hay fever and of sensitization to certain allergens such as ragweed pollen is extremely high among atopic persons it is not surprising that manifestations in parent and child are often the same However statistical analysis indicates that only the atopic tendency is inherited and that closer similarities are due either to chance or possibly to environmental exposure to the same potential allergens

EFFECT OF EXPOSURE TO ALLERGENS

Sources of Exposure —From the moment of birth the child is exposed to a variety of potential allergens in his environment and diet In fact there is suggestive evidence that exposure to food allergens may occur during intrauterine life by the passage of antigens through the placenta from maternal to fetal circulation but conclusive proof of sensitization by this route is lacking If the child is breast fed allergens of foods eaten by the mother may be secreted in the milk in significant amounts As cow s milk and other new foods are added to the diet the possibilities of developing food allergy are greatly increased Progress from the immaculate crib to crawling on the floor increases the variety of inhalant exposures which is further widened as the child spends more time out of doors and comes into contact with pets In the child with the genetic predisposition to atopy particularly if the heredity is bilateral some of these exposures may result in the acquisition of sensitization To some extent the possibility of developing sensitization to specific antigen depends on the sensitizing potential of the antigen and the intensity of exposure but the actual results are capricious and unpredictable at best

Importance of Exposure for Sensitization —Evidence that atopic sensitization results from contact with the allergen is most clearly established in the case of geographically distributed antigens such as pollens In allergy to the pollens of plants of well known distribution it is possible to prove or exclude contact with far greater certainty than in the case of foods and household antigens It has been proved that atopic persons even those with multiple sensitizations do not react on skin test with pollens to which they have never been exposed Coca reported that skin tests with the pollen of ragweed an American plant which does not grow in Europe gave negative results on 35 hay fever patients in Berlin and a group of New York residents with hay fever gave no skin reactions on tests with pollen of Algeroba which is a common cause of hay fever in Hawaii but does not grow in America Phillips has reported that when sugar beets were introduced as a new crop in his area none of the hay fever patients reacted to its pollen but after a few years of exposure there was a considerable incidence of sensitization

The examples cited serve to illustrate the conclusion supported by much other evidence of which space does not permit detailed discussion that both heredity and exposure to allergens are important in determining the develop ment of atopic sensitizations Heredity renders certain persons peculiarly sus ceptible but the acquisition of specific sensitizations depends upon contact with the allergens

Reactions to First Contact—The concept of exposure to antigen as the cause of specific sensitization is more difficult to establish in the case of allergy to foods Occasionally addition of a food often egg for the first time to the diet of an infant may evoke an immediate allergic reaction indicative of pre existing sensitization In the absence of demonstrable previous contact this sensitization was considered by some early investigators to result purely and di rectly from heredity It is now believed to represent allergy developed as a result of exposure to antigen passing through the placenta from mother to child through the milk in the case of breast fed infants or possibly by inhala tion when eggs are cooked handled and eaten by other members of the house hold The most probable source appears to be through the placenta during *intrauterine life but direct proof of this supposition is lacking* Examination of the cord blood of 50 infants with atopic mothers failed to reveal antibodies to common food allergens in any case While intrauterine sensitization might be expected to be manifested in such studies the type of reaction which is be lieved to result from its occurrence is not so common that a series of this size could be considered significant evidence that it does not exist in some instances

On the basis of this belief that sensitization to foods may develop during intrauterine life it has often been recommended that a woman who has pre viously had allergic children limit her diet during pregnancy to avoid the al lergens most commonly affecting infants In the absence of conclusive proof radical restrictions are probably not justified but avoidance of excessive quanti ties of eggs seems a wise precaution

Control of Exposure to Antigens—In the case of children known by family background and by previous atopic disease to be highly susceptible avoidance of unnecessary contact with substances known as potent sensitizers may lessen *the acquisition of new allergies The extent to which one should limit the* activities of a child for this reason must be determined in the individual case but it is apparent that for the highly allergic child foam rubber pillows are more desirable than feather woolen blankets than down quilts and the seashore a better summer environment than hay barns and stables The bringing of cats dogs and birds into the home is fraught with danger of developing sensitization

Nonspecific Factors in the Development of Atopic Sensitization—The irreg ular manner in which the susceptible child becomes allergic to one antigen but not to another with which he apparently has equal contact has already been mentioned This seeming inconsistency has led to the suspicion that the de velopment of sensitization might be favored at times by temporary factors which impaired the defenses of the body against penetration of unaltered an tigen Thus Anderson and Schloss suggested that marasmus in infancy favored sensitization by permitting absorption of milk and egg antigens however their

own subsequent studies indicated that similar absorption of antigen occurred in normal babies

The development of asthma is frequently associated with an acute respiratory infection such as pertussis or pneumonia There is little doubt from the studies of Peshkin and others that symptoms are likely to begin at such a time but it is less clear whether the infection facilitates sensitization or merely precipitates symptoms due to a gradually developed but previously latent sensitization The same is true of tonsillectomy which is frequently mentioned as a precipitating factor in asthma Chemical irritants of the respiratory system are a potent factor in the development of chronic asthma (more often in adults than children) but this form of asthma is rarely associated with atopic sensitization to extrinsic allergens

NATURAL HISTORY OF ATOPIC DISEASE

Since atopic disease results from an apparently hereditary tendency to acquire allergy to antigens with which there is contact and may effect various organs of the body the affected individual may show a succession of different manifestations due to sensitization to different antigens at various ages The course is exceedingly variable many children will never show but one manifestation due to sensitization to a single antigen while others will become allergic to many antigens and show three or four different disease manifestations If the genetic theory of Wiener Zieve and Fries is accepted the former presumably are the persons who have inherited a single allergic factor and the latter are those with a double genetic make up The genetic basis can only be inferred from the observed course but the occurrence of a double dominant factor is obviously more probable in children with a bilateral antecedent history of atopic disease

Efficient management of the allergic child requires an understanding of the succession of developments that may occur so that new symptoms may be recognized in their early stages and appropriate steps taken promptly

The newborn child is generally free of allergic disease but symptoms may appear during the first months of life The commonest initial manifestation is infantile eczema which often begins shortly after the baby is placed on a formula and at least in its early stages often appears to be related to sensitivity to cow s milk orange juice or fish liver oils Substitution of a suitable diet often controls the skin eruption but regardless of the action taken a considerable proportion of these babies outgrow both the disease and the underlying food allergy during the first three or four years of life Others are less fortunate in that skin eruption persists or recurs periodically through childhood and even into adult life as atopic dermatitis When the dermatitis persists additional etiologic factors are apparently involved and simple dietary changes are rarely effective in producing relief

Some infants affected by eczema show evidence of gastrointestinal allergy as manifested by vomiting or diarrhea after certain foods yet it is surprising that this relationship is not more common These same manifestations may occur

in babies not affected by eczema but in such cases their allergic nature is less likely to be suspected

The allergic child is also likely to have frequent head colds and attacks of bronchitis In many cases the recurrent attacks of what appears to be simple infection later prove to be the first manifestations of allergy of the nose and bronchi Asthma may begin in the first year of life or at any age of child hood Nonseasonal allergic rhinitis may become apparent at the age of 2 or 3 years but its recognition as such may take a year or more unless the child is also showing other obvious evidences of allergy Seasonal hay fever is usu ally not recognized before 3 years of age and commonly begins after the age of 5 years The preponderance of respiratory rather than cutaneous and gastro intestinal manifestations is accompanied by the development of allergies to in halant antigens during the period between the ages of 2 and 4 years when many of the early food sensitizations are being lost These sensitizations to pollens and inhalants may be demonstrable in skin tests a year or more before they give rise to clinical symptoms or the symptoms may be apparent a year or more before the test becomes positive

By the age of puberty about one third of the children who have developed asthma in early childhood recover spontaneously but the majority of the un treated cases do not improve and a considerable number become worse Hay fever developed in childhood tends to persist into adult life and if not treated will lead to the later development of asthma in about one third of cases Neglected allergic rhinitis is also likely to result in repeated and chronic nasal infection which predisposes to bacterial allergy manifesting itself in adult life by hyperplastic sinusitis nasal polyps and infective asthma Urticaria and angioedema may effect the allergic child at any age

Realization of this succession of sensitizations to different antigens and vary ing disease manifestations is essential for appreciation of the real nature of atopy It is not to be expected that many allergic children will show all these varia tions but when a baby spontaneously recovers from eczema one cannot assume its atopic tendency has ended Other forms of atopy may be expected to appear later Knowing this probability enables ones to prevent their occurrence in some cases and to recognize their allergic nature more promptly when they do occur

THE IMMEDIATE URTICARIAL SKIN REACTION

One of the characteristic features of atopic disease is the occurrence of an urticarial wheal reaction within ten to fifteen minutes after skin test with the specific allergen The demonstration of such identical skin reactions in hay fever vasomotor rhinitis bronchial asthma infantile eczema atopic dermatitis urticaria and angioedema and many cases of gastrointestinal and cerebral al lergy has strongly supported the concept that these diseases represent manifesta tions of the same type of allergic reaction in different organs of the body

Absence of Skin Reactions in Some Cases—It is important however to realize that such typical skin reactions cannot be demonstrated in all cases of

the diseases mentioned above In typical seasonal hay fever positive skin reactions are demonstrable in almost all cases However in vasomotor rhinitis bronchial asthma urticaria and angioedema gastrointestinal and cerebral allergy there are a considerable number of cases which by all clinical and hereditary criteria appear to be typical atopic manifestations in which the most exhaustive skin tests fail to elicit urticarial reactions

A small proportion of these patients may be shown by careful elimination diets to be clinically allergic to a specific food despite the negative skin reaction In most such cases the symptoms occur three or more hours after ingestion of the causative food Careful studies of a few such patients have shown that they reacted on skin tests with proteoses derived from the digestion of the suspected food and were actually sensitive to antigens formed in its digestion but not active in the original material The frequency with which this explanation is applicable to the association of clinically demonstrable food allergy with a false negative skin test is not known One should also consider the possibility that the extracts used for the skin test may have deteriorated Particularly in the cases of berries and shellfish the antigens are extremely unstable and better results are often obtained by a scratch test with fresh or frozen foods than with any prepared extracts

The Factor of Infection —In the great majority of patients with these diseases who show negative skin reactions elimination diets and environmental changes are not helpful in demonstrating an extrinsic allergen The other possible etiologic factors are discussed in the chapters devoted to the individual diseases but the most common factor in the group as a whole appears to be infection In the patients with the hereditary tendency to atopy bacterial infection may cause the development of a type of bacterial allergy distinct from the tuberculin type and with the same clinical and pathologic manifestations as atopy due to extrinsic allergens However skin tests with the available bacterial antigens filtrates and vaccines do not in general give typical immediate urticarial reactions in such patients Such tests are of no value in diagnosing the etiologic relationship of the infection except in those cases where the accidental use of too strong a skin test dose causes a general flare up of the symptoms of the disease The causative relationship of the infection is more often established on clinical grounds such as the response to antibiotics surgical drainage etc

Whether or not these cases of bacterial allergy are properly included in the category of atopy is a matter of opinion and definition The available evidence does not indicate whether the failure to obtain typical skin reactions is due to lack of the proper type of antigen or whether a different type of mechanism is involved Regardless of the usage of the word such cases form an important proportion of the patients with diseases generally considered as atopic

Atopic Eczema —The preceding discussions also apply to a considerable extent to infantile eczema and atopic dermatitis However the situation in regard to them is more complicated since a large proportion of patients do show positive skin reactions to various allergens both foods and inhalants which do not prove to have any clinical relation to the etiology of the eruption While

such reactions afford evidence of the general relationship of these conditions to atopy they often cause confusion in the etiologic diagnosis This problem will be discussed further in Chapter 13

SKIN SENSITIZING ANTIBODIES

The serum of patients manifesting definitely positive immediate urticarial reactions to skin tests with allergens generally contains antibodies capable of transferring specific passive sensitization to normal human skin The technical details of this procedure the Prausnitz Küstner reaction are described in Chapter 9

Role in Sensitization—Evidence that these antibodies are the actual mechanism of atopic disease is offered by observation of the effects of transfusing blood from atopic donors into nonallergic recipients Ramirez in 1919 reported such a case in which asthma due to horse dander was passively induced in the recipient Loveless has studied in detail the transfer of hay fever by transfusion Within a few hours the skin sensitizing antibody disappears from the circulation of the recipient the skin and eye tests become positive and remain so for weeks indicating a special affinity of the antibody for these tissues Bradel has shown that edema fluid expressed from nasal polyps of atopic persons contains skin sensitizing antibody in far higher concentrations than the serum confirming the presence of the antibody in the shock organ as well as the circulating blood

Properties—The skin sensitizing antibody of atopic persons does not act as a precipitin or passively sensitize guinea pigs Fixation of complement in the presence of antigen is weak and variable if detectable at all The presence of skin sensitizing antibody is demonstrable only in the presence of living cells most commonly by the Prausnitz Kustner phenomenon but also as shown by Katz and Cohen and others by the release of histamine from blood cells when the specific antigen is added to atopic whole blood Practical measures of the amount of skin sensitizing antibody in a sample of serum are made by determining the highest dilution of serum in saline that will produce passive sensitization of normal skin the dilution test

When the skin sensitizing antibody reacts with the specific antigen in the skin some of the antibody is used up so that the same passively sensitized skin site reacts less actively if at all to subsequent tests with the same antigen This neutralization is not entirely specific and a strong reaction to one antigen may affect the subsequent reactions to other unrelated antigens By suitable tests in normal skin the amount of antigen required to neutralize the skin sensitizing antibody of a serum can be determined semiquantitatively

The human skin sensitizing differs from most antibodies in its relative thermolability Heating serum for one half to four hours at 56 C renders it inactive and activity is not restored by the addition of complement

It differs from the anaphylactic antibody of guinea pigs and from most human antibodies in that it does not pass through the placenta from maternal to

fetal circulation This property is of obvious importance in protecting the babies of allergic mothers from passive sensitization in utero

The skin sensitizing antibody also appears to differ chemically from most antibodies which occur in the gamma globulin By Cohn s method of frac tionating sera most of the activity is found in fraction IIID which consists chiefly of beta globulin By various electrophoretic methods of fractionation it has been found in the alpha 2 beta and gamma globulins the location depending on the method used

The many ways in which the skin sensitizing antibody differs from the usual type of antibody lends upport to the view that it is an abnormal antibody produced as a result of hereditary predisposition and distinct from the normal protective antibodies

The observations of Kuhns and Pappenheimer on human diphtheria anti toxin are also consistent with this concept They found that immunization of atopic persons with diphtheria toxoid might produce an unusual type of antitoxin with skin sensitizing properties but lacking the property of flocculating with the antigen which is characteristic of the antitoxin produced by non allergic persons The skin sensitizing antitoxin however possessed the usual antitoxic properties

Absence in Cases Due to Infection —The skin sensitizing antibody has not been found in the serum of those cases of asthma vasomotor rhinitis and urticaria apparently due to bacterial allergy which lack the immediate urticarial skin reaction One may hypothesize that failure to demonstrate antibodies re sults from the type of antigens used in testing but in the absence of supporting evidence the mechanism of this type of bacterial allergy must be considered unknown

IMMUNOLOGIC EFFECTS OF INJECTIONS OF ANTIGEN

Injection Treatment —In asthma and hay fever due to extrinsic antigens that cannot easily be avoided such as pollens mold spores and house dust a considerable degree of relief may be afforded the patient by injection of the causative antigen Such treatment is commonly called *desensitization* but as previously noted in Chapter 2 differs both in practical details and immunologic results from desensitization of the anaphylactically sensitized animal Since the degree of protection produced is only partial the term *hyposensitization* has also been applied while other authors because of the type of immunologic changes produced have suggested that it is more properly designated as *im munization* The details of carrying out such a course of injection treatment are given in Chapter 10 but it may be noted here that a prolonged course of injections of gradually increasing doses of antigen must be given usually once or twice a week until an adequate dose for satisfactory relief is reached This dose is then repeated at intervals of two to four weeks for an indefinite period When treatment is stopped the effects are gradually lost over a period of several months and recurrence of symptoms is anticipated

Effect on Skin Sensitizing Antibody.—The results of the injection treatment do not depend upon elimination or inactivation of the sensitizing antibody. As a rule during the first few months of injection treatment the amount of sensitizing antibody in the circulating plasma is actually increased three- to tenfold. With longer treatment this may return to its previous level or fall below it. The reactions to skin and eye tests with the antigen are usually somewhat decreased during the early months of adequate injection treatment.

Blocking Antibody.—If the serum of a patient receiving injection treatment is studied at intervals by the determination of both the titer of skin sensitizing antibody by the *dilution test and the amount of antigen required to neutralize* the skin sensitizing antibody, the variations in the two tests are not parallel. This indicates a change in the kind as well as the amount of antibody in the serum. Cooke, Barnard, Hebald and Stull have shown that this change involves the development of a *blocking antibody* differing in properties from the skin sensitizing antibodies but reacting with the same antigen.

Properties of Blocking Antibody.—Demonstration of the presence of blocking antibody in the serum of patients receiving injection treatment is greatly facilitated by the observation of Loveless that the blocking antibody is thermostable and essentially unaffected by the degree of heat (4 hours at 56 C.) which completely inactivates skin sensitizing antibody. Therefore if the serum of a treated patient is heated the properties of its blocking antibody may be observed without the interference of the skin sensitizing antibody also present in the unheated serum. The blocking antibody may then be shown to inhibit the reaction of the antigen in sensitized skin and to lessen the activity of antigen in neutralizing the skin sensitizing antibody. In both cases the blocking antibody appears to bind antigen so that it cannot react with the skin sensitizing antibody.

This effect of binding antigen can also be shown in vitro if rabbit serum containing antibodies reacting in vitro with the same antigen is used. Thus the addition of human serum containing blocking antibodies for ragweed pollen inhibits both precipitin and complement fixation reactions of rabbit antiragweed serum with ragweed pollen antigen.

The blocking antibody is not present in the serum of atopic patients who have not received injection treatment. It can be produced experimentally by *injections of pollen extracts with normal nonallergic persons. It does not* passively sensitize human skin or cause anaphylactic sensitization in guinea pigs. When mixed with the specific antigen it does not form a precipitate. Its presence may be detected only by the indirect methods described above.

It differs from the skin sensitizing antibody in other respects than thermostability. Unlike the skin sensitizing antibody but like most other human antibodies it readily passes through the placenta from maternal to fetal circulation. Like most antibodies it occurs in the gamma globulin fraction of the serum. Thus while the skin sensitizing antibody is apparently an abnormal antibody resulting from a hereditary aberration of the immune mechanism, the blocking antibody has many of the characteristics of ordinary protective antibodies.

Protective Effects of Blocking Antibody—Since the blocking antibody has the property of inactivating antigen when mixed with it and its development is the principal immunologic change observed after injection treatment it has been assumed that the benefits of such treatment result from its presence Statistical studies indicate that the titer of blocking antibody is correlated with the development of tolerance in the allergic patient for increasing doses of injected antigen but do not show a clear relationship between its titer and the degree of suppression of clinical symptoms of hay fever by the injection treatment Perhaps these observations may be related to the fact that the blocking antibody is known to be present in the blood stream where it affords protection against injected antigen but nothing is known of its presence in the mucosa of the respiratory system which are in direct contact with inhaled antigens and are the shock organs in the disease While further studies are needed to elucidate the role of the blocking antibody in the relief of allergic symptoms by the injection treatment this uncertainty does not reflect doubt as to the efficiency of such treatment which was well established clinically before the presence of the blocking antibody was demonstrated

PHYSIOLOGY OF ATOPIC REACTIONS

The Role of Histamine—The principal manifestations of atopic disease—dilatation of small blood vessels edema resulting from transudation of fluid through capillary walls increased secretion of the mucous glands and smooth muscle spasm—resemble the pharmacologic effects of histamine

To some extent the manifestations of allergic disease can be reproduced in the nonsensitive person by injection of histamine Experiments of this type in human subjects have been limited to relatively small doses because of the intense throbbing headache produced by larger amounts The typical wheal and erythema reaction of the intracutaneous test with antigens is readily reproduced in the nonallergic person by the intracutaneous injection of minute amounts of histamine After intramuscular or intravenous injection of moderate doses general flushing and a feeling of heat in the skin is produced but not the typical appearance of discrete urticarial wheals with itching

Moderate doses of histamine do not reproduce the symptoms of asthma in normal persons but in persons subject to asthma and free of symptoms at the time small doses may produce an attack Similar attacks may also often be induced in persons previously subject to asthma by injection of Mecholyl a derivative of acetylcholine The exact relationship of such experimentally produced attacks to naturally occurring asthma remains obscure since the symptoms produced by histamine are readily controlled by antihistaminic drugs and those produced by Mecholyl by atropine but neither type of drug separately nor the combination of both is particularly effective in the treatment of clinical asthma

Effects of Antihistamine Drugs—Additional evidence of the role of histamine in atopic disease is offered by the inhibiting effects of antihistamine drugs on the reactions The urticarial reaction to skin tests with specific antigens is markedly inhibited by adequate doses of antihistamine drugs given just before the test

Most cases of acute urticaria and seasonal hay fever are relieved to a considerable degree by these drugs The effects on bronchial asthma are far less marked These clinical observations are confirmed by the studies of Schild and his associates on isolated allergic bronchial muscle They found that the in vitro reaction of sensitive muscle with antigen was inhibited by antihistamine drugs only in high concentrations approximately 10 000 times the concentration required to inhibit the stimulation of the same muscle preparation by histamine itself In atopic eczema also antihistamine drugs have little effect

Release of Histamine—Studies by Katz and Cohen and other authors have shown that when the whole blood of a patient with hay fever is mixed with the specific protein antigen outside of the body a measurable amount of histamine is released from the cells into the plasma Furthermore excised lung and bronchial tissue from a patient with atopic asthma was shown by Schild to release histamine when antigen was added to the perfusion fluid These studies leave little doubt that histamine is released during the allergic reaction However studies of the plasma histamine levels of patients during acute attacks of atopic disease and during free intervals have failed to show a consistent increase associated with the occurrence of symptoms Such patients show wider fluctuations in their plasma histamine levels than normal persons but the occurrence of symptoms may be accompanied by an actual decrease in the plasma level

It is apparent that the evidence relating histamine to the atopic diseases is somewhat less complete than in the case of anaphylaxis but still impressive The differences may be due in part to the fact that the atopic reaction is usually limited to a single shock organ while anaphylaxis is an overwhelming systemic reaction Histamine produced locally in the shock organ may cause symptoms without affecting the general plasma level and produce different manifestations than histamine absorbed into the circulation from a distant injection site

It is possible that histamine is only one of a number of physiologically active agents involved in the phenomena of atopy The well established use of antihistamine drugs in the atopic diseases would tend to indicate that histamine plays an important part

Effects of the Nervous System—In the past many writers have believed the nervous system to play a predominant role in the physiology of atopic diseases Many atopic reactions resemble somewhat the motor effects of the parasympathetic nervous system but few are effectively controlled by atropine which is a specific inhibitor of parasympathetic stimuli The previously cited work of Schild conclusively shows that nervous action is not essential in producing the spasm of bronchial musculature in asthma the only type of atopic reaction which has been subjected to such detailed physiologic study

THE CONSTITUTIONAL REACTION

The clinical manifestations of most atopic diseases are confined to a single shock organ the nasal mucosa in hay fever the bronchial tree in asthma etc Often these are the organs most heavily exposed to the antigen in the natural

exposures However the occurrence of positive skin tests in patients with respiratory allergy and the presence in their blood of sensitizing antibodies are indications that the sensitization is by no means limited to the shock organ which reacts in the usual symptoms The generalized nature of the sensitization becomes apparent when an excessive dose of antigen is inadvertently injected into a highly allergic patient during skin testing or injection treatment producing a *general* or *constitutional reaction* Such general reactions are also occasionally seen when a patient eats a food to which he is highly allergic

The precautions in skin testing and treatment to be described in detail in following chapters are of the greatest importance in avoiding such reactions However if a considerable number of allergic patients is handled occasional constitutional reactions will inevitably be encountered and it is essential that the physician be thoroughly familiar with their manifestations and treatment

Etiology

The occurrence of a general reaction depends upon enough antigen entering the circulation to produce reactions in shock organs remote from the site of injection If an antigen is accidentally injected into a vein rather than into the subcutaneous tissue such spread is greatly facilitated and a severe reaction may result from a dose which would be well tolerated if properly injected More often the reaction simply reflects a dose that is too large for the degree of allergy of the particular patient Certain antigens are known to produce these extreme degrees of sensitization more frequently and this is reflected in the dilutions recommended for the initial intracutaneous tests However the differences between individual patients are as great or greater than those between antigens so that alert caution is necessary in using any antigen

During the course of injection treatment the development of blocking antibody in the circulating plasma helps to protect the patient against constitutional reactions by inactivating antigen which enters the circulation Increasing tolerance for antigen noted as treatment progresess reflects an increasing titer of blocking antibody but too large a dose will exceed the degree of protection When the doses given for treatment are increased in a logical manner the tolerance may be exceeded but marked overdosage should not occur

The most severe reactions are likely to result from the initial skin testing rather than treatment for at this time the physician has no previous knowledge of the patient s tolerance to guide him Since the dilution which is needed to elicit a skin test in one allergic child may be ten or even a hundred times that which will be tolerated by another care and judgment is essential The practical details of procedures are discussed in Chapter 9

Symptoms

Constitutional reactions may occur within a few minutes after the injection or after a latent period of one hour or more Most of the severe reactions are apparent within twenty minutes

The manifestations of a constitutional reaction vary according to its severity In the less severe cases a sudden flare up of the usual symptoms of the allergic disease may be the only manifestation Flushing itching and swelling of the skin particularly of the face and hands and urticaria starting around the site of the injection and becoming generalized are common manifestations Sneezing tearing redness and swelling of the conjunctivae are also frequent Coughing wheezing dyspnea and cyanosis may occur in patients who have not previously had asthma

In the more severe cases the symptoms resemble those of anaphylactic shock with circulatory failure pallor syncope and coma These circulatory features may follow the symptoms noted in the preceeding paragraph or occur within a few minutes of the injection and be the only symptoms Death may occur either from circulatory shock or from asphyxia

In most cases the skin test or injection causing the general reaction is marked by a large local reaction but occasionally almost immediate circulatory failure may inhibit the development of the local reaction

Treatment

Whenever skin tests or allergen injections are done the physician must be prepared to cope with a constitutional reaction This means that a rubber tourniquet epinephrine hydrochloride 1 1 000 solution and a sterile syringe for injecting it should be readily available Intracutaneous tests and injections of allergens should always be given in the arm or leg at a site which permits effective application of the tourniquet proximal to their location The patient should always wait in the office twenty minutes after an injection to permit observation of the reaction

If any symptoms of a constitutional reaction appear the tourniquet should be promptly applied between the site of the injection and the body tight enough to prevent the flow of venous blood but not the flow of the arterial circulation It is kept in place until the symptoms are controlled by treatment

Since it is impossible to tell at the onset how severe a reaction may prove to be treatment should be prompt and active The most effective drug is epinephrine because of its speedy action Antihistamine drugs and cortisone have some value but should not be relied upon as the sole medication because of slower action As soon as the tourniquet is applied epinephrine 0 1 to 0 5 ml depending on body weight and the apparent severity of the reaction should be injected intramuscularly above the tourniquet or in another extremity The same dose may be repeated every 5 or 10 minutes if necessary until the symptoms are relieved After one or two injections of epinephrine it may be supplemented by an injection of an antihistamine drug such as Benadryl 10 to 20 mg or Chlor Trimeton 5 to 10 mg

Circulatory failure should be treated by injection of nikethamide (Coramine) 1 ml or caffeine sodium benzoate 0 3 to 0 1 mg per pound of body weight intramuscularly or intravenously Cyanosis calls for the inhalation of oxygen if available

If suitable treatment is given at once most reactions are controlled within ten minutes After the tourniquet has been released the child should remain in the office ten or fifteen more minutes to be sure there is no return of symptoms and to allow the side effects of epinephrine to pass If the reaction has been moderate or severe an oral antihistamine may be given at this time and re peated if necessary after four hours

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Chapter 8

ALLERGENS CAUSING ATOPIC DISEASES

INHALANT ALLERGENS

In the causation of allergic disease of the respiratory system a major part is played by antigens inhaled as dust suspended in the air Practically all of these dusts are typical protein antigens from animal or plant sources The possibility of solid material being suspended in the air so as to be inhaled depends on the particles being of small size and relatively low density on the velocity and turbulence of air currents and on the humidity of the air

Some idea of the fate of inhaled particles of various sizes may be gained from the studies of therapeutic aerosols summarized by Abramson In general particles more than 30 microns in radius are removed from the inhaled air by *the nasal turbinates or settle in the trachea particles 10 to 30 microns in radius* the size of most allergenic pollens are largely deposited in the bronchi while particles of 3 to 10 microns reach the alveolar ducts Those 1 to 3 microns in radius reach the alveoli but a large percentage of those 0 5 microns or smaller are exhaled

Certain biologic dusts such as pollens and mold spores are by nature of relatively uniform particle size On the other hand dust derived from the crumbling of organic material such as feathers consists of particles of a great range of sizes

In considering the inhaled allergens it is logical to describe separately the pollens which follow definite geographic distribution and seasonal occurrence and the nonseasonal allergens which may be encountered without definite limitations of seasons or geography

Animal Danders —All fur bearing animals shed epithelial scales which are of suitable particle size to act as inhaled allergens so that any animal to which

the child is exposed particularly inside a building home or barn must be considered a potential cause of allergic symptoms Obviously dogs and cats are the most frequent offenders but in the case of farm children cows horses pigs and sheep may be considered Rabbits may be important as pets or because of the use of their fur in mittens coat collars etc Hamsters guinea pigs and chinchillas may occasionally be encountered Since the dander becomes incorporated in the house or barn dust direct contact with the animals is not essential for the occurrence of symptoms and in houses infested with rats or mice these may cause allergy

The material inhaled consists of microscopic epithelial scales and not the visible hair but since both are shed together the presence of dog or cat hairs on carpets upholstered furniture or clothing is presumptive evidence of epithelial dust There is no doubt that some animals of each species shed considerably more dander than others To some extent this parallels the amounts of hair shed The question is often raised whether different breeds of dogs differ in the antigenicity of their dander There is no conclusive proof of antigenic differences between breeds of the same species and on biologic grounds it appears probable that differences in the symptoms noted after exposure to dogs of various breeds result from variations in the amount of dander shed rather than its specificity

The proteins of the dander muscle (meat) and serum of each species are antigenically related although not identical Thus allergy to horse dander is almost invariably accompanied by a degree of sensitivity to horse serum which is extremely serious if antiserum derived from horses must be injected for therapeutic purposes The saliva of dogs and cats also contains antigens related to those of the dander so that allergic children may have symptoms from being licked by pets

It is obvious that human beings as well as lower animals shed dander different individuals shedding quite different quantities Certain allergic persons especially those affected by atopic dermatitis show typical wheal reactions to intracutaneous tests with extracts of human dander The nature and significance of this reaction has not been established No evidence of specific antigenic differences between the dander of different persons has been established The vague reports of allergy of one individual to another have not been proved to have an antigenic basis the influence if real is more probably psychologic

The antigens of animal danders are readily extracted with alkaline saline fluids to yield suitable solutions for skin tests In the case of horse dander ample quantities of material are readily available but it is rarely possible to obtain adequate amounts of dry dander from smaller animals including dogs and cats These extracts are usually made from clippings or fur which yield satisfactory extracts of dander but their potency must be measured by chemical determination of protein or total nitrogen since the quantity of hair used for extraction is not a true index of the amount of dander

The principal treatment of allergy to animal danders is avoidance of exposure to the antigen When this is impossible and in cases of marked sensitization *where the child has symptoms from unavoidable indirect contacts in*

jection treatment may be considered Treatment with injections of animal dander antigens is comparable to that with pollen extracts in the doses used the results obtained and the risk of undue reactions

Feathers—Allergy to feathers is extremely common because of the widespread use of feathers and down in pillows quilts and upholstered furniture The highest grade of these products is filled with goose down but chicken duck and goose feathers are used interchangeably in those of ordinary qualities With age the feathers become more brittle and increasing amounts of dust sift through the fabric covers

The feathers of each of these birds differ somewhat in antigenic specificity but there is considerable cross reaction between the species Since the species of feathers to which a child is exposed is often uncertain differentiation between them is of limited value Satisfactory results may be obtained by the use of a mixture of equal parts of extracts of chicken duck and goose feathers in the diagnosis and treatment of allergy to the feathers used in bedding and furniture

Exposure to other birds—canaries parakeets etc—should be considered separately and skin tests made with an extract of the particular species if there is contact

Because of the intimate contact with a feather pillow even slight degrees of allergy shown by skin tests may be presumed to be important in the causation of respiratory allergy A one plus reaction to an intracutaneous test with an extract containing 1 000 P N * units per milliliter is adequate reason to end the exposure Feather beds and down quilts should be replaced with wool or cotton blankets no form of cover for them can be relied upon to retain the antigenic dust In the case of feather or down pillows dustproof coverings of rubberized or plasticized fabric may suffice if the child is only slightly allergic They are useful when traveling since they are more readily carried than a special pillow For the child who is moderately or markedly allergic to feathers it is best to change to a foam rubber or Dacron pillow for regular use Kapok pillows are less desirable from the standpoint of durability and occasionally induce sensitization in a child who did not react to kapok when the change was made If a brother or sister sleeps in the same room with the patient the same precautions should be taken with both beds

Furniture upholstered with feathers or down should be removed from the child s bedroom but elimination of such furniture from other rooms in the house is rarely essential

Because of the relative ease of avoiding contact injection treatment plays a relatively small part in the handling of feather allergy The feather antigen is quite suitable for treatment of moderately or markedly allergic children who will be exposed to furniture upholstered with down but cannot be expected to produce a degree of immunity which will permit the use of a feather pillow It rarely produces excessive reactions and may be readily combined with dust allergen in the treatment of patients allergic to both

Fabrics—The protein fibers wool and silk are potential allergens they play a relatively small part in respiratory allergy but may be a factor in skin

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* Protein nitrogen unit (see page 109)

allergy The cellulose vegetable fibers cotton and flax and the synthetic fibers are not antigenic although artificial finishes and dyes applied to them occasionally cause contact dermatitis The allergen extracts ordinarily used in skin tests for wool and silk allergy are prepared from crude raw materials and reactions to them do not necessarily imply the occurrence of symptoms from contact with finished fabrics The wool extract usually contains sheep dander which is thoroughly removed from the fiber in the manufacture of cloth Ordinary woolen fabrics may cause contact dermatitis but rarely are a cause of respiratory allergy A skin test reaction to wool does not prevent the wearing of woolen clothes although it is wise to avoid direct contact of wool with the skin in cases of dermatitis Rough woolen fabrics such as blankets and sweaters are more apt to cause trouble by carrying house dust than by their own antigenicity Woolen blankets may be used but should be covered with a cotton spread or sheet Children reacting to the silk antigen may have symptoms from relatively crude silk fabrics such as pongee but rarely from highly finished silk cloth Small articles of finished silk such as neckties are negligible as a cause of respiratory symptoms

Vegetable Seeds — A number of different vegetable seeds contain proteins which may act as potent antigens Among these are cottonseed kapok seed flaxseed and the castor bean While allergy to these is not very common the degree of sensitization is apt to be marked

Cottonseed may be present in traces sufficient to cause allergic symptoms in cheap cotton mattresses and upholstery but rarely in the better quality products Cottonseed flour is widely used in the making of doughnuts and may cause symptoms either as an inhalant when the child enters the shop or as a food when the doughnut is eaten Cottonseed oil as prepared for use in cooking is believed to be free of the antigen Cotton cloth is also free of the antigen Cottonseed meal is a common ingredient of animal feeds to which farm children may be exposed Kapok seed is almost invariably present in kapok pillows and mattresses so that their use should be avoided in the environment of a child allergic to this antigen Flaxseed is used in toilet preparations poultices and in flaxseed tea as a home remedy Castor bean pomace is an ingredient of commercial fertilizers Mustard while important chiefly as a food may act as an inhalant when used in mustard plasters

All of these vegetable seeds may act as potent antigens and great care is necessary in using them for skin tests if severe reactions are to be avoided The physician with limited experience in allergy may prefer to use them only for scratch tests When they are used for intracutaneous tests one must be alert for points in the history suggestive of allergy to them The normal strength of cottonseed kapok flaxseed and mustard allergens for intracutaneous testing is 10 P N units per milliliter but if the history suggests specific allergy to them an extract containing one unit per milliliter should be used first Extracts of castor bean are not recommended to be included among the routine inhalant tests as allergy to it is relatively rare in children If there is an indication in the history of allergy to commercially mixed fertilizer an intracutaneous test may be done with an extract (boiled to remove the toxic protein ricin which is present in the castor bean) containing 0 1 P N units per milliliter If neces

sary this may be followed by a test with 1 unit per milliliter extract care being taken not to inject more than 0 02 ml in each test

The use of any of these seed antigens for injection treatment entails a serious risk of constitutional reactions and should not be attempted except by physicians with wide experience in the field

Vegetable Gums —Acacia (gum arabic) karaya gum and gum tragacanth are rather widely used for technical purposes and in prepared foods and may act as inhaled or food allergens These are essentially complex carbohydrates but the commercial preparations contain some nitrogen It is believed that the carbohydrate acts as an antigen but evidence to exclude a nitrogenous protein antigen is not conclusive They are used as adhesives on labels and envelopes in hair and skin lotions tooth pastes and powders mouthwashes as excipient in certain pills and tablets and in some types of chewing gum In preparation of foods they are used as stiffening agents in gumdrops and other candies in pastries ice cream cream cheese and salad dressings For further details see the *reference to Gelfand*

For intracutaneous tests extracts containing 1 per cent of these gums by weight are suitable Sensitization is not common and excessive reactions to skin tests are unusual Conclusive evidence of the efficiency of injection treatment with these antigens is lacking so that an attempt to avoid contact is the best procedure in treating sensitive children However because of the varied uses in many of which the three gums mentioned may be used interchangeably strict avoidance is difficult

Pyrethrum —The dried blossoms of pyrethrum a plant of the composite family are frequently used in insecticides both as a dry powder and in sprays and aerosols Since it is quick but transitory in its action it is often combined with D D T and other slow acting persistent insecticides Pyrethrum is not toxic but is moderately allergenic acting both as an inhalant in the causation of respiratory allergy and as a skin sensitizer in the causation of contact dermatitis In intracutaneous tests for inhalant allergy it may safely be used in a relatively strong concentration (1 000 P N units per milliliter)

Orris —Formerly a common ingredient of face powder and other cosmetics orris is less often used in recent years because of its activity as an allergen It is *still* included in some brands of cosmetics *particularly those that are imported* from Europe and the use of such preparations by the mother may be a cause of allergic symptoms in children Skin tests may be performed with extracts containing *100 P N* units per milliliter *Avoidance is easily accomplished by the* use of nonallergic cosmetics which are certified not to contain this ingredient

Tobacco —Another potential allergen present in most households but of relatively little importance in pediatric practice is tobacco Allergen extracts are prepared from the dried leaf and used for intracutaneous tests in dilutions containing 1 000 P N units per milliliter Positive reactions suggest the avoidance of contact with the leaf there is no conclusive evidence that the smoke contains significant amounts of the allergen although it obviously acts as a nonspecific irritant in many children with respiratory allergy

Molds and Fungi — Among the most important causes of respiratory allergy *in children are mold spores They are present in the outdoor air during the* warm months of the year in numbers comparable to or occasionally even greater than pollen grains indoors throughout the year and in the case of Candida (Monilia) may grow as saphrophytes in the mouth and respiratory system Molds are abundant in the upper layers of the soil dead leaves and other vegetation hay stacks barns and stables Although the spores may be spread many miles by winds and are present everywhere they are usually more abundant in *rural and wooded areas Unlike the pollens the atmospheric mold spores do not* have a definite seasonal incidence but are present in amounts varying with wind and weather conditions in all months when the temperature remains above the freezing point

Throughout North America Alternaria and Hormodendrum are by far the most abundant and allergenically the most important atmospheric molds Among the other genera which are commonly present are Aspergillus Candida Cephalo*thecium Dematium Helminthosporium Mucor and Penicillium All of these* are potential allergens but the number of patients sensitive to Alternaria and Hormodendrum exceeds those reacting to all the others

Most of these same fungi may be readily cultured also from indoor house dust No house is free of mold spores but their prevalence indoors varies greatly with the location humidity ventilation type of construction and cleanliness Damp cellars and basements dusty attics and houses or rooms which have been closed *and developed a musty smell are obviously heavily infested* Old mattresses pillows and other bedding which have not been aired recently are rich sources *Some idea of the prevalence of molds in a house or room may* be gained by exposing a Petri dish containing Sabouraud s medium for five to ten minutes but the actual number of colonies developing under these conditions will vary depending on the air currents and the extent to which activities have raised the dust The number and variety of molds grown in such cultures is usually amazing and their identification requires considerable training in mycology

Allergen extracts of molds may be used for intracutaneous skin tests in dilu*tions containing 100 to 1 000 P N units per milliliter Because of the prevalence* of allergy to Alternaria and Hormodendrum tests for these two molds should be included in the routine study of children with nonseasonal or summer respiratory allergy Tests with the other molds are far less rewarding but the physician devoting much time to pediatric allergy should have extracts at least of Aspergillus Candida Cephalothecium Dematium and Mucor for testing of children with atypical symptoms and those reacting to either Alternaria or Hormodendrum In regard to skin tests with Candida it should be noted that children who have had moniliasis of the skin or other organs usually give a delayed inflammatory *reaction of the tuberculin type* to intracutaneous tests with Candida allergen This reaction which becomes evident after twenty four hours bears no relation to the immediate wheal reaction *which is evidence of atopic sensitization* or to the causation of respiratory allergy

Attention to ventilation control of humidity and cleanliness may help to decrease the indoor exposure to mold spores and air conditioning or window

filters may lessen the exposure to outdoor atmospheric molds. However, a degree of avoidance satisfactory to prevent symptoms usually is not feasible. Therefore injection treatment with molds, particularly Alternaria and Hormodendrum, is frequently necessary. If a patient shows skin reactions to a large number of the molds, a mixture of several may be used for treatment. It is well to remember that the heaviest exposure is usually to Alternaria and Hormodendrum and to be sure that adequate doses of at least these two are given. Dosage of mold allergens is essentially similar to that in which pollens are used. In general they are well tolerated, but occasional children will be found to be highly sensitive, particularly to Alternaria, so that care must be taken in progressing the dosage.

House Dust.—One of the most important factors in respiratory allergy is the antigenic mixture which can best be described as house dust. A large proportion of children with respiratory allergy have exacerbations of symptoms when dust is raised indoors by sweeping or similar activities. Evidence that this results from specific allergy rather than mechanical irritation is furnished by positive skin tests to extracts of house dust. This dust is largely derived from partially disintegrated fibers of fabrics, feathers and other organic materials in the furnishings contaminated with hair and dander of household pets, and with a wide variety of mold spores and bacteria. The skin reaction to extracts of this mixture reflects to some extent allergy to these ingredients. However, many allergic children show reactions to extracts of house dust which cannot be explained by comparative tests with any of the original materials known to contribute to the composition of the dust. This different antigenicity is believed to result from chemical changes of the materials in the process of aging and disintegration.

Chemical studies have failed to satisfactorily explain the source or nature of the distinctive antigen or antigens in the dust extract, but the empiric use of extracts of house dust as allergens in the diagnosis and treatment of respiratory allergies has proved to be of great practical value.

The antigenicity of dusts from different houses varies somewhat, but in general those from houses in one area, where the same general type of furnishing is used, are relatively similar. On the other hand, dusts from tropical countries differ quite markedly from those of temperate climates. For the preparation of antigen solutions a pool of samples from vacuum cleaners in a number of residences in the locality is used, avoiding those heavily contaminated with known allergens, such as dust from houses where there are pets, and samples collected during seasons of heavy pollination. Samples from houses where toxic insecticides have been used are also avoided. The pooled dust is defatted with a suitable solvent and saturated with alkaline extracting fluid. The resultant solution is dialyzed to remove irritants of low molecular weight and sterilized by filtration. There is no satisfactory standard of potency because of the nature of the material; determinations of the protein nitrogen content are of questionable significance, but an extract which shows 10,000 protein nitrogen units per milliliter may be considered a suitable concentrated solution for the preparation of dilutions used in intracutaneous testing and treatment. Extracts falling

much below this arbitrary standard may be concentrated by evaporation in tubes of semipermeable plastic membrane. Dust antigens for use in scratch testing must be highly concentrated by chemical methods such as those described by Boatner and Efron used in the preparation of Endo dust.*

In a great majority of allergic children extracts of pooled dust from houses in the general locality are quite satisfactory for testing and treatment. However, in cases where the history is suggestive of dust allergy and the skin reactions to stock extracts are slight, or in which there are symptoms strikingly related to a certain house but not accounted for by skin reactions to known allergens such as pets, the preparation of an extract of dust from the patient's own house may be advisable. Such a special dust extract may be prepared from a pint to a quart of packed dust from a vacuum cleaner. It should always be compared with the stock dust allergen in skin tests on the patient since a single sample of dust does not always yield a satisfactory extract. For the method of preparing dust extract, see the Appendix.

POLLEN ALLERGENS

The pollens of plants comprise one of the most important groups of allergens causing respiratory allergies. As the germ cells of the plants, they are rich in protein and probably the pollens of all species contain potential allergens. However, a few pollens which are very abundantly produced are notably inactive as causes of allergy, such as the cattail and pine pollens. The latter apparently does not readily cause sensitization because of the presence of a relatively impervious outer coating which resists the passage of soluble proteins into surrounding moisture.

Most pollinating plants are cross fertilized, so that the pollen of one plant must reach the ovum of another of the same species to enable the seed to develop. The two main means of transfer of pollen from one plant to another are by the wind and by insects. Plants which are adapted to wind pollination in general have inconspicuous flowers and produce a large amount of light bouyant pollen grains, usually 15 to 50 microns in diameter, which may be blown for miles from their source. Those adapted to insect pollination have showy, fragrant flowers and produce relatively small amounts of heavy, sticky pollen which does not blow about. It is the pollens of the wind pollinated plants that are most important in the causation of allergy because of the large amounts of pollen produced and its wide distribution. However, many of the insect borne pollens are active antigens and may produce symptoms if there is adequate exposure through handling the flowers or bringing them into the house.

The wind borne pollens of the temperate zones include most of the common trees, all grasses, and a considerable variety of weeds. All of these, except the cattails, pines, and the related conifers, must be considered potential allergens. For practical purposes in allergic diagnosis and treatment it is unnecessary to deal separately with each *species* of pollen. The pollens of each *genus* of trees and weeds may be considered essentially similar and handled by using the pollen of

* Manufactured by Endo Products, Inc.

the commonest species of the genus in the area as a representative Thus the pollen of red oak may be expected to react similarly to the pollens of all other oaks but not to cross react with birch

Without undue botanical detail it may be noted that the genus Carya includes hickory and pecan and the genus Acer maple and box elder Several of the genera of weeds include a number of different species which produce hay fever in various parts of the country but which are presumably not familiar to the physician without special interest in botany The genus Amaranthus includes pigweed careless weed and spiny amaranth the genus Artemisia sage mugwort and wormwood the genus Atriplex saltbush wing scale and shad scale and the genus Franseria rabbit bush bur ragweed false ragweed and beach sandbur In each genus the use of the species most common in the area suffices for testing and treatment

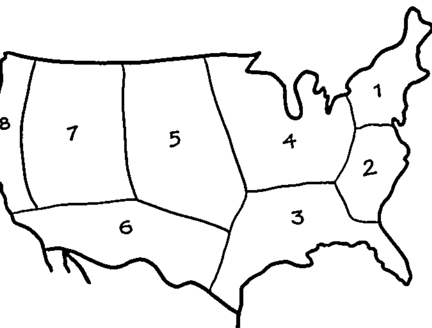
Patients sensitive to one grass usually react quite similarly to grasses of other genera and there is evidence that treatment with the pollen of one grass confers some degree of protection against others Satisfactory results may be expected if a mixture of three or four of the grass pollens most important in the area is used in testing and treatment for all grasses

Each plant causing hay fever has a definite season for producing pollen which varies in different areas but is almost constant in each area from year to year Weather and growing conditions affect the amount of pollen produced in a given year, but have relatively little effect on the time it is liberated In order to treat hay fever a practical knowledge of the plants producing wind borne pollens in the area and of their seasons of pollination is essential

In the present volume only a brief listing of the principal pollens causing hay fever in various parts of the United States will be given More detailed information may be obtained from books of Wodehouse of Vaughan and Black and of Samter and Durham The last of these includes information on pollens in Canada Cuba and Mexico Dozens of local studies have been made in various parts of the United States References to many of these are given by Wodehouse and by Vaughan and Black

The physician devoting much of his time to treatment of allergic diseases will profit from learning to recognize the principal hay fever producing plants so that he can observe their abundance *and time of pollination in his area Identification of pollen grains caught on exposed* slides requires much greater training in botany and is scarcely a necessary task for physicians practicing in areas which have previously been carefully studied

Because of the great variations in the flora and seasons of pollination in various portions of the United States it may be divided into eight zones for purposes of discussion Since most of these zones *are relatively large, not all* of the pollens mentioned for each zone are important in all parts of it and seasons of pollination may vary somewhat in different parts of the same zone This is particularly true of Zone 3 the Gulf States and Zone 6 the Southwest



F g ? —Pollen zones of the U ited States

TABLE IV

ZONE 1 NEW ENGLAND AND MIDDLE ATLANTIC STATES

POLLEN	SEASON
Elm	April
Poplar	April
Maple	April Ma
Birch	April May
Oak	May
A I	May
Sycamore	May Ju e
H ckory	May June
Plantain	May June
Sorrel	May June
Grasses	June July
Ragweed	August September

The princ pal grasses are timothy orchard and June grass There are areas essentially free of ragwee l in the northern parts of New York and New Hampshire and the wooded sections of Maine

TABLE V

ZONE 2 SOUTH ATLANTIC STATES

POLLEN	SEASON
Alder	February
Elm	February March
Cedar	February March
Box Elder (Maple)	February April
Ash	March April
Poplar	March April
Birch	March April
Oak	April May
Walnut	April May
Sycamore	April May
Hickory (Pecan)	April May
Grasses	May July
Ragweed	August October

The principal grasses are Bermuda Johnson June timothy and redtop

TABLE VI

ZONE 3 THE GULF STATES

POLLEN	SEASON
Cedar	February March
Elm	February March
Poplar	March April
Birch	March April
Oak	March April
Hickory (Pecan)	April May
Grasses	April November
Amaranth	June September
Marsh Elder	September
Ragweed	September October

The principal grasses are June Bermuda and Johnson In Southern Florida the seasons of pollination are greatly prolonged the grasses pollinating through most of the year Australian pine of the genus Casuarina not a true pine is a factor in Southern Florida The Miami area is relatively free of ragweed

TABLE VII

ZONE 4 THE MIDDLE WEST

POLLEN	SEASON
Elm	March April
Maple (Box Elder)	March May
Birch	April May
Ash	April May
Poplar	March April
Oak	May
Sycamore	May
Hickory	May June
Plantain	May June
Grasses	May August
Amaranth	July September
Chenopod	July September
Russian Thistle	July September
Sage (and other Artemisiae)	July September
Marsh Elder	August September
Ragweed	August September

The principal grasses are timothy June orchard and blue Western water hemp hemp and Kochia are important in some parts of the zone This is the area of heaviest ragweed pollen but some areas in the northern parts of Michigan and Minnesota are relatively free

TABLE VIII

ZONE 5 THE GREAT PLAI

POLLEN	SEASON
Alder	March
Box Elder (Maple)	March April
Elm	March April
Oak	April May
Plantain	May July
Grasses	May July
Chenopod	May September
Amaranth	June August
Kochia	July August
Russian Thistle	July August
Western Water Hemp	July August
Hemp	July September
Sage (Wormwood)	July September
Cocklebur	August September
Ragweed	August September
Marsh Elder	August October

The principal grasses are timothy June blue orchard and redtop

develop slowly [illegible] protein in a food is not a significant f[illegible] [illegible]rawberries which [illegible] per cent protein act as an allergen more often [illegible] in the meats [illegible] to 20 per cent.

Milk.—The [illegible] milk in the diet of infants and children is ob[illegible]ous Adapted [illegible] as the complete nourishment of the new born it also [illegible] children a richer source of nutritional factors re quired for gr[illegible] than any other article of the diet. I[illegible] one of the m[illegible] which to find a satisfactory natural subst[illegible] but artif[illegible] soybean or meat proteins have been prepared to [illegible] properties of milk.

About [illegible] the protein of milk is casein which is the c[illegible]able [illegible] production of cheese The remaining whey fra[illegible]tion contains [illegible] small amount of lactoglobulin and traces of other protei[illegible] usually considered together in the di[illegible] gnosis of allergy Th[illegible] allergy to the normal proteins of human milk, although [illegible] that traces of foreign protein contained in the mother's die[illegible] in the milk and cause allergic reactions in the infant [illegible] of eczema is very low so long as an infant is purely [illegible]ted

Allergy to cow's milk [illegible]mmon during the first year of life and in the great ma[illegible] of cases end spontaneously before the age of 4 or 5 years. While the allergic manifestations are varied and often severe violent immediate reactions to milk are [illegible] general reactions to intracutaneous tests are rare and dilution [illegible] 1 000 to 10 000 PN units may be used routinely. The reaction is m[illegible] often to the whey fraction than to the casein The protein of this fraction is readily altered by heat and heating destroys its allergenicity for many affected infants In some cases the relatively mild heat to which canned evaporated milk has been exposed suffices in others boiling the milk is adequate Casein is relatively heat stable and its antigenicity is not appreciably affected by boiling

The mammalian milk most readily available as an alternative to cow's milk is goat's milk which is equally suitable for human nutrition although older children may find the flavor objectionable unless it is disguised It is sold fresh in some localities but is generally distributed in canned form The casein of goat's milk is antigenically closely related to that of cow's milk while its whey proteins differ in specificity As a rule infants allergic to cow's milk whey can tolerate goat's milk while those with the less common allergy to cow's milk casein cannot There are exceptions in both cases and if passive transfer tests are done in cases of milk allergy it is well to te[illegible] the casein and whey of the milks of both species

If neither cow's or goat's milk is toler[illegible] most [illegible] substitute in infant nutrition is an emu[illegible] of [illegible] of [illegible] brand are available in canned for[illegible] is [illegible] unre[illegible] [illegible]k to milk and rarely acts as an [illegible] ally [illegible] al factors as cow's milk and [illegible] nt f[illegible] but is less easily digested [illegible] so

TABLE VII

ZONE 4 THE MIDDLE WEST

POLLEN	SEASON
Elm	March April
Maple (Box Elder)	March May
Birch	April May
Ash	April May
Poplar	March April
Oak	May
Sycamore	May
Hickory	May June
Plantain	May June
Grasses	May August
Amaranth	July September
Chenopod	July September
Russian Thistle	July September
Sage (and other Artemisiae)	July September
Marsh Elder	August September
Ragweed	August September

The principal grasses are timothy June orchard and blue Western water hemp hemp and Kochia are important in some parts of the zone This is the area of heaviest ragweed pollen but some areas in the northern parts of Michigan and Minnesota are relatively free

TABLE VIII

ZONE 5 THE GREAT PLAINS

POLLEN	SEASON
Alder	March
Box Elder (Maple)	March April
Elm	March April
Oak	April May
Plantain	May July
Grasses	May July
Chenopod	May September
Amaranth	June August
Kochia	July August
Russian Thistle	July August
Western Water Hemp	July August
Hemp	July September
Sage (Wormwood)	July September
Cocklebur	August September
Ragweed	August September
Marsh Elder	August October

The principal grasses are timothy June blue orchard and redtop

TABLE IX

ZONE 6 THE SOUTHWESTERN STATES

POLLEN	SEASON
Mountain Cedar	January February
Elm	February March
Poplar	February March
Ash	March April
Oak	March April
Walnut	March May
Franseria	March October
Mesquite	April July
Grasses	April October
Amaranth	May September
Atriplex	June September
Kochia	June September
Russian Thistle	June September
Sage	July October

The principal grasses are timothy Bermuda June Johnson and brome The variations in plants and seasons is particularly great in different parts of this zone True ragweed is not a significant factor

TABLE X

ZONE 7 THE MOUNTAIN STATES

POLLEN	SEASON
Alder	March April
Cedar	March April
Poplar	March May
Maple (Box Elder)	March May
Birch	April May
Oak	*April June*
Plantain	May July
Grasses	May July
Russian Thistle	July September
Kochia	July September
Amaranth	July September
Chenopod	July September
Sage	August September
Ragweed	August September

The principal grasses are timothy redtop blue and brome In this zone ragweed is one of the less important weeds

TABLE XI

ZONE 8. THE PACIFIC NORTHWEST

POLLEN	SEASON
Alder	February-April
Elm	February-April
Cedar	February-May
Sycamore	March-April
Poplar	April
Birch	April
Maple (Box Elder)	April-May
Oak	April-May
Walnut	April-May
Grasses	April-September
Plantain	May-September
Franseria	May-October
Atriplex	June-September
Sage	July-September
Chenopod	August-September
Ragweed	August-September

The principal grasses are blue, orchard, timothy and velvet. Ragweed is a very minor factor in this zone.

FOOD ALLERGENS

Essentially all natural foods contain some protein and are potentially antigenic. To a considerable extent the body is protected against absorption of antigenic proteins from the intestine by the processes of digestion and metabolism in the liver, which reduce the bulk of the ingested protein to amino acids which are not antigenically active. It has been suggested that the relatively high incidence of food allergy in infancy, as compared to adult life, may be due to incomplete development of these defenses. On the other hand, it may be readily demonstrated that significant amounts of at least some food proteins pass into the peripheral circulation of normal adults in an allergenically active form. If a site in the skin of such a nonallergic adult is passively sensitized by the intracutaneous injection of 0.1 ml. of the serum of a patient highly allergic to an active allergen, such as egg white or peanut, subsequent eating of the specific food will produce a typical wheal reaction at the sensitized site, usually within 20 to 30 minutes.

Whether or not the above explanation is valid, allergy to foods is most common in infancy and early childhood; a large proportion of the children thus affected lose their food sensitivity spontaneously as they grow older. Food allergy in young children may be manifested by cutaneous, respiratory, gastrointestinal, and occasionally neurologic symptoms. In severe cases asthma, generalized urticaria, vomiting, and diarrhea may occur together within a few minutes after eating the allergenic food. More often, the symptoms are of more gradual onset and affect only one of the shock organs.

Certain foods, such as eggs, nuts, fish, and shellfish, are rather common causes of the sudden severe reactions, while such staple items of the diet as meats, milk, cereals, and the common vegetables usually cause symptoms which

develop slowly The amount of protein in a food is not a significant factor strawberries which contain 0 8 per cent protein act as an allergen more often than the meats which contain 15 to 20 per cent

Milk —The importance of milk in the diet of infants and children is obvious Adapted by nature to serve as the complete nourishment of the newborn it also supplies to older children a richer source of nutritional factors required for growth and development than any other article of the diet It is one of the most difficult foods for which to find a satisfactory natural substitute but artificial mixtures containing soybean or meat proteins have been prepared to essentially duplicate the nutritive properties of milk

About 75 to 80 per cent of the protein of milk is casein which is the coagulable fraction used in the production of cheese The remaining whey fraction contains lactalbumin with a small amount of lactoglobulin and traces of other proteins all of which are usually considered together in the diagnosis of allergy There is no evidence of allergy to the normal proteins of human milk although it has been suggested that traces of foreign protein contained in the mother s diet may be secreted in the milk and cause allergic reactions in the infant In general the incidence of eczema is very low so long as an infant is purely breast fed

Allergy to cow s milk is common during the first year of life and in the great majority of cases ends spontaneously before the age of 4 or 5 years While the allergic manifestations are varied and often severe violent immediate reactions to milk are unusual general reactions to intracutaneous tests are rare and dilutions containing 1 000 to 10 000 P N units may be used routinely The reaction is more often to the whey fraction than to the casein The protein of this fraction is readily altered by heat and heating destroys its allergenicity for many affected infants In some cases the relatively mild heat to which canned evaporated milk has been exposed suffices in others boiling the milk is adequate Casein is relatively heat stable and its antigenicity is not appreciably affected by boiling

The mammalian milk most readily available as an alternative to cow s milk is goat s milk which is equally suitable for human nutrition although older children may find the flavor objectionable unless it is disguised It is sold fresh in some localities but is generally distributed in canned form The casein of goat s milk is antigenically closely related to that of cow s milk while its whey proteins differ in specificity As a rule infants allergic to cow s milk whey can tolerate goat s milk while those with the less common allergy to cow s milk casein cannot There are exceptions in both cases and if passive transfer tests are done in cases of milk allergy it is well to test with the casein and whey of the milks of both species

If neither cow s or goat s milk is tolerated the most widely used substitute in infant nutrition is an emulsion of soybean protein of which several brands are available in canned form This is completely unrelated antigenically to milk and rarely acts as an allergen It offers essentially the same nutritional factors as cow s milk and has long been used for infant feeding in the Orient but is less easily digested and often causes diarrhea and sore buttocks

Similar mixtures of meat protein with oil carbohydrate and calcium salts which approximate the composition of milk are also available They are usually well taken by infants and are less apt to cause diarrhea than the soybean preparations Feeding the allergic infant on meat protein introduces the theoretical possibility of causing sensitization to the meat but the available evidence does not indicate that this has occurred in practice

Casein hydrolyzates (Nutramigen) which have been digested artificially until they are not antigenic also offer a safe substitute for milk in preparation of infant formulas This material is usually well tolerated but the taste may be objectionable to older children

Children allergic to milk should avoid cream skimmed milk buttermilk butter and ice cream all of which contain the same antigens Butter substitutes prepared from soybean are available Ordinary oleomargarine contains milk protein and is not suitable Those allergic only to the whey fraction may tolerate natural cheese but not process cheese to which a considerable proportion of lactalbumin is usually added during manufacture The small amount of milk protein in commercial white bread causes symptoms only in the most sensitive children

Eggs --Egg is one of the most antigenic of the common foods Allergy to it is common in infancy and childhood often disappears spontaneously but may persist into adult life Skin gastrointestinal and respiratory symptoms may be produced and are not infrequently of the violent immediate type occurring within a few minutes after ingestion Allergic infants may react promptly the first time egg is added to the diet suggesting that sensitization has been acquired by passage of the antigen through the placenta or breast milk Schloss has shown that the addition of egg to the diet of an infant is commonly followed by the development of circulating antibodies indicating antigenic activity which may or may not be accompanied by clinical symptoms

Both the white and the yolk are rich in protein that of the white consisting chiefly of albumin with small amounts of conalbumin ovomucoid and ovomucin that of the yolk chiefly of ovovitellin with a small amount of livetin Allergy to the proteins of the white is considerably more common than to those of the yolk The two groups of proteins are antigenically different but egg yolk separated by the usual home methods is apt to be contaminated with egg white

The proteins of egg are denatured by heat and cooking lessens their antigenicity to a greater or less degree depending on the method used However the acutely sensitized child is usually unable to tolerate them in any of the usual forms including cooked mixtures such as custard and cake

Aside from its potential antigenic properties egg (particularly the yolk) is an excellent food for growing children exceeding milk as a source of iron and vitamin D All of its nutritional factors however may be provided from other sources Because of its potency as an antigen it is wise to postpone its addition to the diet in the case of infants with allergic symptoms or a family history of allergy until an age of 12 months when the danger of sensitization is considerably decreased

Because of the frequency of violent sensitization general reactions to skin tests with egg proteins are not unusual If the child is eating eggs without obvious reaction the routine intracutaneous test should be made with not more than 100 P N units per milliliter 1 or 10 units if the history is suggestive of allergy to egg

Allergy to egg yolk is also important because of the common use of virus and rickettsial vaccines prepared from cultures on egg yolk These include typhus Rocky Mountain spotted fever and influenza virus vaccines They must not be given to children known to be allergic to egg yolk In doubtful cases an intracutaneous test with a 1 10 dilution of the vaccine should precede the injection

Meats —Sensitization to the usual meats beef lamb pork chicken and turkey is not common but sufficiently frequent to warrant consideration The flesh of each species is antigenically different but coincidental allergy to two or more of the group may occur The allergic manifestations are rarely violent and skin tests may be done with extracts containing 1 000 P N units per milliliter Delayed clinical reactions associated with a negative skin test have been reported These must be detected by dietary trials but are apparently not common

Fish and Shellfish —In contrast to the meats fish protein is highly allergenic and severe acute reactions are not unusual Some children show a group sensitivity reacting to all types of bony fish and to fish glue made from them while others may react to a single species or several closely related species It *appears probable that the group reaction to fish may occasionally* be acquired by exposure to fish glue as an inhalant

Because of the possibility of an extreme degree of sensitization intracutaneous tests with fish antigens are best avoided in children whose history is strongly suggestive of such allergy If they are considered necessary in such cases the method of passive transfer is advised If direct tests are done the intracutaneous test should be preceded by a scratch test with extracts not stronger than *1 000* P N units per milliliter If this gives no reaction the intracutaneous method may be used cautiously starting with an extract containing 1 P N unit per milliliter

Since the clinical reaction to fish is usually obvious children who are eating fish without apparent symptoms from it may be tested intracutaneously with extracts containing 100 to 1 000 P N units per milliliter For routine tests it is common practice to use a mixed antigen containing several species representative of the commonly eaten types such as salmon tuna cod flounder and halibut

Avoidance of fish is relatively easy synthetic vitamin preparations being used in place of those derived from fish liver oils

Antigens of *shellfish* are distinct from those of the true fish but also may cause severe sensitization The antigens of crab shrimp and lobster are related but not identical the same is true of the mollusk group which includes clam oyster and scallop Intracutaneous tests with any of these antigens carries a certain risk of constitutional reaction and if the history is suggestive may be avoided entirely done in passive transfer or preceded by a scratch test

On the other hand extracts of shellfish are relatively unstable and rapidly alter so that some children with a definite clinical allergy fail to react to skin tests with the best available extracts In this case a scratch test with the fresh or frozen material is more significant than the intracutaneous test with prepared extracts

Grain Products —Foods derived from the grains wheat corn rice rye barley and oats play an important part in the usual diet of childhood as bread cake crackers cereals spaghetti etc Allergy to one or more of the group is not unusual but rarely of extreme degree Intracutaneous tests with solutions containing 1 000 P N units per milliliter are relatively safe but not entirely reliable Slight or moderate (one plus to two plus) reactions usually prove to be without clinical significance and all positives should be confirmed by dietary trials Occasionally fairly definite clinical sensitization may be accompanied by a negative skin test

Most children allergic to corn protein tolerate corn starch and corn oil (Mazola etc) without symptoms Avoidance of the various grains presents no serious problem except in the case of wheat Wheat flour is widely used in cooking to thicken sauces gravies etc and it is used in the production of most rye bread Pure rye bread is obtainable in some localities and Ry Krisp is carefully kept free of wheat for use as a bread substitute in wheat free diets

Fruits —Among the commonly eaten fruits several botanical families are represented These relationships are indicated in Table XII Fruits in each family have some tendency to cross reactions in allergy In skin testing with fruits it is well to include at least one fruit from each family that the child eats If a patient reacts to the fruit which is tested the possibility of reaction to others of the same family must be considered

All of the fruits mentioned in the table are occasional causes of allergic symptoms Among the most frequent offenders are the citrous fruits banana melons and berries of the rose family (Rosaceae) The symptoms may be immediate in nature but are rarely violent

Skin tests may be made with extracts containing 1 000 P N units per milliliter with little danger of a constitutional reaction unless there is a definite history of sensitization to the specific food Positive reactions should be confirmed by trial diets as many prove to be of doubtful significance The extracts of berries and to a less degree of other fruits are relatively unstable and occasionally even relatively fresh extracts may fail to react on an obviously allergic patient If such a false negative reaction is suspected a scratch test with the juice of the fresh or frozen fruit should be tried

Avoidance of even a number of different fruits offers no serious problem although supplementary vitamin C may be considered advisable if the intake is severely restricted

Vegetables —Like the fruits the familiar vegetables belong to a number of botanical families as indicated in Table XII There is some tendency to multiple sensitizations within the same botanical family but this relationship is less marked in instances where a different portion of the plant is eaten as in potato and tomato

TABLE XII

BOTANICAL CLASSIFICATION OF FOODS DERIVED FROM PLANTS

MONOCOTYLEDONS	
Family	
Gramineae	Barley corn oats rice rye wheat
Palmaceae	Cocoanut date
Bromeliaceae	Pineapple
Liliaceae	Asparagus garlic onion
Musaceae	Banana
DICOTYLEDONS	
Family	
Moraceae	Fig mulberry
Polygonaceae	Buckwheat rhubarb
Juglandaceae	Pecan walnut
Chenopodiaceae	Beet spinach
Cruciferae	Broccoli cauliflower cabbage mustard radish turnip
Rosaceae	Blackberry raspberry strawberry
Pomaceae	Apple pear
Drupaceae	Almond apricot cherry peach plum
Leguminosae	Beans pea peanut soybean
Rutaceae	Grapefruit lemon orange
Vitaceae	Grape
Malvaceae	Cottonseed (flour) okra
Sterculiaceae	Chocolate cocoa
Umbelliferae	Carrot celery parsley parsnip
Convolvulaceae	Sweet potato
Solanaceae	Eggplant potato tomato
Cucurbitaceae	Cantaloupe cucumber melon squash
Compositae	Endive lettuce

All of the vegetables are potential causes of allergy but peas beans tomato potato and carrots are among the commonest offenders The manifestations are rarely violent and the risk of intracutaneous testing with extracts containing 1 000 P N units per milliliter is not great Many of the smaller skin reactions obtained are not clinically important and should always be confirmed by dietary trials

Skin tests are ordinarily done with extracts of raw foods and in the case of vegetables always eaten in the cooked form the alteration of antigenicity in cooking may explain some of the false positive skin reactions This difficulty may be partially overcome by testing with extracts that have been boiled one hour in a water bath but no single heating procedure can accurately parallel the various methods of cooking the same vegetable At best the skin tests with vegetables offer only clues to be confirmed by the history and a rational basis for further investigation by elimination diets

Nuts—The nuts while rarely forming a major part of the diet are important in allergy because of their tendency to cause violent immediate reactions Peanuts are the most important of the group because of the wide use of peanut butter Peanut oil is also much used but there is no evidence that it causes allergic symptoms even in children sensitive to peanuts Almonds pecans walnuts filberts coconut Brazil nuts and chestnuts are also to be considered Although these familiar nuts represent a half dozen different botanical families group reactions to nuts are fairly common

Because they are usually eaten sporadically and the allergic reactions are often immediate the history is a relatively reliable index of sensitization If the history is positive skin tests are scarcely necessary but if they are done a scratch test or passive transfer test should precede cautious intracutaneous tests If the child eats the various nuts without apparent symptoms intracutaneous tests may be done with extracts containing 100 to 1 000 P N units per milliliter

Spices —Of the spices mustard is the most important cause of allergy in children Like the nuts it may be the cause of violent immediate reactions and should be used with great care in skin testing The routine strength for intracutaneous testing if the history is negative is 10 to 100 P N units per milliliter Cinnamon cloves nutmeg black pepper thyme and sage are less important They may be tested intracutaneously with extracts containing 100 to 1 000 P N units per milliliter

Miscellaneous —Chocolate and cocoa powder made from it by partial defatting are fairly common causes of allergy during childhood The manifestations are most often of the delayed rather than the immediate type and alarming reactions to ingestion or to skin tests are rare It may be used for intracutaneous tests in a strength of 1 000 P N units per milliliter Some of the delayed reactions to chocolate are associated with negative skin tests and must be evaluated by clinical observation In interpreting the statement of the parent the physician should bear in mind that the importance of chocolate as an allergen is exaggerated in the minds of many people to a degree that frequently leads to unjustified suspicion

Vegetable gums acacia tragacanth and karaya gum which have been discussed among the inhalant allergens are widely used in commercially prepared foods as thickening and stiffening agents often as a substitute for egg white Among the foods which may contain them are candies pies and other pastries icing of cakes ice cream cream cheese sauces gravies and salad dressings

Cottonseed also classed with the inhaled allergens is used as cottonseed flour in the preparation of commercial doughnuts Cottonseed oil is widely used in cooking but does not contain the cottonseed allergen

Substitute Foods —The substitutes for milk in infant feeding have already been discussed Avoidance of other foods during infancy and childhood is a less difficult problem When the diet is markedly restricted the physician must be careful that the supply of all the essential nutriments for growth is adequate In the case of the vitamins suitable concentrates are readily available An ample amount of protein may require positive suggestions as to substitutes for the foods eliminated Suitable information is available in *Allergy Cooking* by M L Conrad and *The Allergic Patient and His World* by F E Sammis Both of these books are intended for use by the mother in planning menus and recipes Useful suggestions are also supplied by the Ralston Purina Co

ANTIGENIC SOLUTIONS FOR TESTING AND TREATMENT

Preparation —In general the antigens causing atopic disease are soluble in water or slightly alkaline aqueous solutions and the antigen preparations

used for intracutaneous testing and injection treatment are made by extracting the material with fluids containing sodium bicarbonate or a phosphate buffer The methods of preparation must be varied according to the nature of the raw material In some cases dialysis is necessary to remove irritating impurities Bacteria are removed by passage through a Seitz or similar filter and the sterility of the extract established by cultures Phenol (0 01 to 0 5 per cent) or glycerin (up to 50 per cent) are added as preservatives Since it is difficult to compare allergen extracts and no government standards of purity or potency have been established it *is essential to obtain them from a reputable manufacturer*

Multiple Antigens —The extracts of most natural allergens are mixtures of several different potential antigens and often a considerable amount of aller genically inert material For example ragweed pollen which has been ex tensively studied in this respect contains at least three proteins of different antigenic specificity Various patients with ragweed hay fever react differently to these potential antigens essentially all reacting to one about a half to the second and relatively few to the third While all of these are present in the ordinary extracts used for testing and treatment the responses of individual patients vary somewhat depending on their reactivity to these different com ponents

Deterioration —Most of the antigen extracts gradually lose their potency the rate of deterioration varying with different antigens In general pollen ex tracts lose 50 to 60 per cent of their potency in the course of one year at refrig erator temperature and much more rapidly at room temperature Extracts con taining *50 per cent glycerin are far more stable Such extracts are too irritating* for intracutaneous tests and rather painful for injection Concentrated ex tracts may be preserved in this manner if they are diluted at least tenfold before use so that the material injected contains not more than 5 per cent glycerin These dilutions however deteriorate at approximately the same rate as extracts made without glycerin All allergen extracts should be kept re frigerated as much of the time as possible and in general a fresh supply should be obtained annually If patients are treated throughout the year with the ordinary extracts made without glycerin it is essential when changing from year old to fresh extracts to adjust the dosage to allow for 50 to 60 per cent *deterioration*

Standardization —No uniform method of measuring and expressing the potency of allergen extracts has been adopted This makes it difficult to com pare extracts from various sources and particularly to change from one make of extract to another in the course of injection treatment In some cases the strengths are expressed merely as dilutions of the concentrated extract which gives no real basis of comparison since the methods of preparation are not standard This method is not satisfactory except in the case of extracts of house dust allergen which are not susceptible of exact standardization

There are three methods of measuring potency in common use (1) by the weight of material extracted with a given volume of fluid (2) the total ni trogen content of the extract as determined by the Kjeldahl method and (3) the protein nitrogen content usually determined by precipitation with phos

photungstic acid Since all three methods give results in cumbersome dilutions or decimals arbitrary units have been proposed for expressing the results in whole numbers The *Noon pollen unit* is defined as the antigen extracted from 0 001 mg of dried pollen the *total nitrogen unit* represents 0 00001 mg of total nitrogen and the *protein nitrogen unit* (Cooke and Stull) 0 00001 mg of protein nitrogen

Since these units are based on different types of standardization it is im possible to establish any fixed ratio between them When pollens of different species are extracted the amounts of both total and protein nitrogen obtained from a gram of pollen vary considerably To a less extent the amount of nitrogen and protein extracted from pollen of a single species will vary with different batches of pollen with the care taken in drying and storing the pollen before extraction with the type of extracting fluid and with the details of the process of extraction A typical extract prepared from 5 grams of *low ragweed* pollen with 100 ml of bicarbonate extracting fluid usually contains about 0 54 mg of total nitrogen and 0 18 mg of protein nitrogen per milliliter This might be expressed as a 5 per cent extract a 1 20 dilution or as containing 50 000 Noon pollen units 54 000 total nitrogen units or 18 000 protein nitrogen units per ml A typical 5 per cent extract of *timothy grass* pollen (50 000 Noon pollen units per milliliter) may contain 0 46 mg of total nitrogen per milliliter (46 000 total nitrogen units) and 0 27 mg of protein nitrogen (27 000 protein nitrogen units) It is apparent that in the case of ragweed and timothy pollens the Noon pollen unit roughly equals one total nitrogen unit and one half protein nitrogen unit This is equally true in the case of most other prin cipal grass pollens but cannot be assumed to apply to tree and other weed pol lens In all cases the results obtained will vary with different batches of pollen and variations in the extracting procedure With pollens of some plants the results may be quite different especially in the case of a pollen such as pine which is not easily extracted by the routine methods

In the case of substances other than pollens particularly mixtures from which only a minor portion may be extracted the weight/volume standard is essentially worthless For example in preparing dander extracts of dogs cats and other small animals it is customary to use a considerable amount of clipped hair from which a small amount of dander antigen is extracted In such cases the amount of hair used is no measure of the dander and determination of either the total or protein nitrogen is essential in order to judge potency

In the belief that the protein nitrogen offers the best practical measure of activity it is used in this book for all allergen extracts except house dust in which the chemical nature of the allergen is unknown and vegetable gums in which it is uncertain whether the antigen is carbohydrate or a nitrogen com pound House dust is used on a simple dilution basis and the vegetable gums which are readily obtained in a pure soluble form on the weight/volume basis

It is apparent that the doses in protein nitrogen units recommended for injection treatment in Chapter 10 cannot be exactly converted into Noon units or total nitrogen units but the physician using allergens standardized by either

of these methods can readily follow the same general principles basing the initial doses on the reaction to intracutaneous tests made with the same extracts he used in the injection treatment

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Chapter 9

DIAGNOSIS OF THE SPECIFIC CAUSATIVE ALLERGENS

Importance of Specific Diagnosis — The diagnosis of allergic diseases implies the existence of one or more specific causative agents or allergens to which the patient is reacting In the atopic diseases such allergens may be inhaled dusts foods drugs or infectious agents Many patients react to several different allergens of the same or different types It is usually possible to obtain temporary relief of allergic symptoms by nonspecific drugs such as antihistamines and steroid hormones but these drugs have no curative effect Except in such self limited allergic conditions as *drug and serum reactions recurrence of symptoms is almost* certain after the drug is discontinued Satisfactory control of symptoms over a period of time depends on detection of the causative agent so that suitable measures of avoidance or specific treatment may be undertaken Therefore the diagnosis of allergic disease cannot be considered complete until the causative agent or agents affecting the individual patient are determined Because of the frequency of allergy to multiple factors the establishing of a single cause gives no assurance that others may not be important and the specific diagnostic survey must consider all of the more probable agents which might logically produce the type of symptoms from which the child suffers The extent of such a study will depend on the time and circumstances under which attacks occur Allergic disease which is strictly seasonal will require the consideration of fewer possible agents than that which occurs throughout the year

In evaluating the factors that precipitate attacks in the individual child it is important to differentiate between the fundamental allergenic causes which induce the sensitization and secondary factors which may be the immediate

causes of attacks in the sensitive person These secondary factors include many causes of irritation of the shock organs as well as changes in its physiologic activity Thus attacks of respiratory allergy may be precipitated by cold dampness sharp odors of chemical fumes paint turpentine tobacco smoke or by any activity which increases the depth of respiration Acute respiratory infections may act as primary causes in children with bacterial sensitization or as secondary factors in those sensitive to inhalants Manifestations of skin allergy may be aggravated by overheating sweating hot baths contact with wool tight clothing rubbing or scratching Both respiratory and skin allergies may be made worse by emotional stresses which appear to act as secondary factors affecting persons whose disease is primarily due to specific agents The avoidance of nonspecific secondary factors contributes to the control of allergic disease but they should not be mistaken for the basic causes of sensitization

Methods of Specific Diagnosis —Determination of the specific causes of allergy *depends upon the correlation of the clinical history the physical examina*tion and suitable aid from x rays and cultures for the detection of infections and tests for sensitization No reliable in vitro tests for atopic sensitization are available the reactions must be observed by applying antigen to living tissues By these means it is in most cases possible to arrive at an etiologic diagnosis in the course of a few visits In some instances this initial survey must be supplemented by a longer period of observation during which the effects of change of diet or environment are noted before arriving at a final diagnosis For the diagnosis of food allergy various types of elimination diets or the food diary method may be helpful In the evaluation of inhalant factors the environmental test may be useful

The nonspecific secondary factors which act as precipitating causes of attacks in the sensitized child are not antigens Attempts to use those that are material substances in skin tests are ineffectual Unlike specific allergens they may be expected to affect most children with allergic diseases to a greater or lesser degree Their importance in the individual case can only be judged from the history and by observation

CLINICAL HISTORY

In the study of known or suspected allergic diseases a careful and complete history is the first and one of the most important steps in diagnosis Since the same history serves both to establish the existence of allergic disease and to guide the determination of the specific causative agents it must combine the features of a general pediatric history with a number of points particularly applicable to the differential diagnosis and specific diagnosis of allergic disease The detail required will vary in different types of allergic disease but in general time spent on taking a careful history will be well repaid In simple cases due to a single allergen the history may practically establish the diagnosis In more complicated cases with multiple sensitizations it will suggest possible causes indicate sensitizations so marked that special care must be taken in doing intra

cutaneous tests furnish a reasonably complete list of the potential allergens with which the child is in contact so that these may be included in the series of skin tests and also indicate the part played by nonallergic secondary factors. The form of the history may well vary with the individual case the following discussion is intended to indicate the type of material particularly applicable to allergic diseases.

Because of the familial tendency to atopic disease the family history is of value in suggesting the probability of such disease in the child. The occurrence of asthma hay fever infantile eczema atopic dermatitis urticaria due to foods or definite gastrointestinal allergy in the parents or siblings is significant. The history of such diseases affecting the grandparents and collateral relations is suggestive. Aside from seasonal hay fever the identification of allergic rhinitis in such a family history is often difficult many cases of nonseasonal rhinitis being reported as catarrh or sinusitis. Urticaria due to serum or penicillin and chronic urticaria of unknown cause cannot be safely assumed to indicate an atopic tendency. Some authors have included migraine among the group of atopic diseases no doubt some cases are due to food allergy but in the absence of definite proof a history of migraine in the family is best disregarded as evidence of atopy. Contact dermatitis is not one of the atopic diseases and its occurrence in the family has no bearing on the probability of atopy in the child.

Even more important is the history of previous manifestations of atopic disease in the child being studied. From the previous discussions it is apparent that children who have one of the atopic diseases are very prone to develop other diseases of the group. The development of recurrent head colds with frequent sneezing in a child who has had infantile eczema is sufficiently suggestive of an underlying allergic rhinitis to warrant careful study and frequent recurrences of bronchitis in an atopic child suggest the gradual development of asthma.

The past history should include a record of immunization procedures and of any reactions resulting from them. This is particularly important with regard to diphtheria and tetanus whether toxoids have been used for active immunization and whether the antitoxins have been needed. Drugs which have been used should also be noted with mention of any allergic reactions produced by them. Since the diagnosis of drug allergy depends primarily on the history adequate details of the symptoms time relations and consistency of the reactions are essential. Specific inquiry concerning the use of penicillin and the sulfonamides should be made and any reactions noted.

The dietary history should include data on feeding during infancy with a record of any obvious intolerance. In addition notes should be made of the dietary habits foods taken in unusual amounts or avoided because of dislike or apparent intolerance. If a food is not well tolerated inquiry should be made as to the exact nature of the symptoms produced and the time after ingestion. Often the parent's statement that a child is allergic to a particular food is based on previous medical advice which may subsequently prove to

be erroneous rather than actual observation of symptoms after eating it. In evaluating whether or not the reaction to food is allergic it is well to note whether it occurs after all forms of the same food. If a child will not tolerate milk but takes ice cream freely, allergy can hardly be suspected. Specific inquiry should be made whether each of the principal groups of foods are taken: milk, eggs, cereals, meats, fish, shellfish, vegetables, fruits, nuts, chocolate and mustard. The more active food allergens such as egg, fish, shellfish, nuts and mustard should not be tested by the intracutaneous method unless they are known to be eaten by the child without an obvious allergic reaction. Listing the meats, vegetables, cereals, and fruits taken regularly is also helpful in the selection of skin tests.

The physical environment of the child is of obvious importance in relation to inhaled allergens. Concerning the residence it is important to know whether it is a house or apartment, new or old, located in the city, suburbs, or country. The type of heating is of interest as hot air ducts often are a source of dust. Special features of the location such as dampness, proximity to barns, stables or factories may be important. Exposure to pets, horses, and farm animals should always be noted. Occasionally rats or mice in the house may be an unsuspected cause of allergy.

The bedding is equally important. The type of pillow and mattress stuffings should be noted and also whether blankets, quilts, or comforters are used and the nature of the filling in the latter. If dust appears to be a factor the type of carpets, draperies, and other furnishings of the child's room are of interest.

The account of the present illness should include full details of the onset, whether abrupt or gradual, the season, location, and circumstances, and relation to unusual activities or acute infectious diseases. Subsequent attacks should be noted as to frequency, duration, seasonal or diurnal variation, and relations to location, diet, activities, and other illnesses. The medications used for relief are important as indications of the severity of symptoms. Notes concerning previous allergic studies and specific treatment are of obvious interest. The occurrence of constitutional reactions to tests or injections is particularly important. In general one should not be deterred from carrying out the indicated studies by the results of previous tests as the sensitivities of children may change over a period of a few years. History of previous ineffectual injection treatment does not mean that a more logical program may not succeed, but the history of constitutional reactions should be a warning to proceed carefully in testing and treatment.

The impressions of the parents of the child as to the cause of attacks should be considered. Often these will refer simply to nonspecific precipitating causes, but occasionally they may yield a valuable clue to the basic allergens.

SKIN TESTS

The immediate wheal and erythema reaction characteristic of the atopic diseases results from the introduction of a small amount of antigen into the

active layers of the skin This may be accomplished by the *scratch test* in which antigen is applied to a scratch penetrating the cornified layer of the skin the *puncture test* in which a needle is passed into the skin through a drop of antigen solution on its surface or the *intracutaneous test* in which a small volume of antigen solution is injected into the superficial layers of the skin

Both the scratch and intracutaneous tests are extensively used in allergic diagnosis Each method has certain advantages which lead some physicians to use it exclusively although other physicians employ both The puncture method has been less widely used and for purposes of discussion may be considered a modification of the scratch test

Both the scratch and intracutaneous methods involve risk of general reactions due to the absorption of too much antigen by a highly allergic patient This risk is far greater when the intracutaneous test is used Fatal reactions have resulted from the scratch test and a considerably larger number from the intracutaneous test Many of the latter occurred during the relatively early years of allergic diagnosis and may be attributed to the use of testing materials and methods that would not be considered acceptable at present Several were due to the use of strong extracts of allergens now recognized to be dangerous others to performance of tests on the back of the patient so that a tourniquet could not be used to control the reaction With standardized extracts and proper precautions the danger of severe reactions is greatly reduced but is still greater with the intracutaneous than the scratch method

The scratch test requires very little equipment and utilizes dried or relatively stable concentrated antigens The intracutaneous method requires a number of sterile syringes and the use of suitable allergen dilutions which are relatively unstable These are practical considerations if only an occasional patient is tested

On the other hand far more exact information is obtained by the intracutaneous test A considerable number of reactions which are clearly apparent on the intracutaneous test may be missed by the scratch technique Since there is less trauma to the skin and the positive reactions are larger the difference between a positive and a negative reaction is far more definite when the intracutaneous test is used The intracutaneous test also gives a wider range in the size of positive reactions permitting some estimate of the degree of allergy Finally the intracutaneous method permits the use of various different dilutions of the antigen to confirm or further evaluate a positive reaction while in the scratch test a concentrated antigen is usually needed to produce any reaction

If the full benefit of skin tests is to be realized the intracutaneous test should be used in the final study The scratch test may be used as preliminary procedure on children believed to be usually sensitive to certain antigens or when dealing with new and unfamiliar antigens The routine performance of a large number of scratch tests followed by intracutaneous tests with many of the same antigens which has been advised by some authors prolongs the testing program out of proportion to the gain in safety However the physician who chooses to use the intracutaneous test as a routine must be fully aware of the

possibility of general reactions be familiar with the clinical history of eacl tient he tests choose the antigen dilutions to be used carefully on the bas the patient s history and his own general experience and carefully observe necessary precautions The physician who performs skin tests only rarely well be content to rely mainly on the scratch test

The Scratch Test

Technique—The scratch needed to bring allergen into contact with living layers of the skin may be made with virtually any type of needle suc a Hagedorn needle a large darning needle or a hypodermic needle atta to a small syringe as a handle A small scalpel preferably not too sharp as a chalazion knife is also suitable The scratching instrument is sterilized each patient but not for each scratch

Most physicians employing the scratch test perform the tests on the b Since this location does not permit the application of a tourniquet in case general reaction its use lessens to some extent the safety which is the c reason for using the scratch test rather than the more delicate intracutan test If the physician is using the scratch test only for patients or antigens wl he believes the risk of reaction to be particularly great he should perform th like intracutaneous tests only in sites on the extremities which permit effec application of a tourniquet proximal to the tests The anterior aspects of arms and thighs are most suitable

The skin to be tested is cleaned with alcohol or a nonstaining antise solution The skin is stretched and held tense between the thumb and fin of the left hand and a series of scratches at least one inch apart are made w the point of the needle or knife The scratch should be about 6 mm long d enough to penetrate the cornified layer of the skin but not to draw blood

If powdered antigens are used a drop of N/10 sodium hydroxide solutio placed on each scratch Each antigen is then applied to one scratch with a cl flat toothpick mixed with the alkaline fluid and rubbed into the scratch allergen solutions are used these are applied directly to the scratch with cl toothpicks In either case one scratch is treated only with diluent as a cont A fresh toothpick must be used for each antigen The amount of fluid used sho be sufficient so that the tests remain moist until read

Reading the Scratch Test Reactions—The reactions to scratch tests read after twenty to thirty minutes There is no established standard evaluating the results In many cases the skin shows some edema along control scratch and in patients with dermatographia the control reaction m be considerable In any case it represents the negative reaction and posit reactions are evaluated by comparison with it Any distinctly greater react is recorded as one plus a wheal without pseudopods is classed as two plus a mm wheal with pseudopods as three plus and larger reactions four plus

The Intracutaneous Test

Technique—The intracutaneous test is performed by injecting a small volume of a suitable dilution of sterile allergen extract into the superficial layers of the skin This is most easily accomplished by the use of a 1 ml tuberculin or allergy type syringe with a 26 gauge needle Since the allergen extract is withdrawn from rubber capped vials by passing the needle through the cap it is most practical to use ¼ inch needles The use of longer needles of 26 gauge requires great care in puncturing the rubber caps if excessive destruction of needles by bending is to be avoided When the tests are performed it is essential to have at hand a solution of epinephrine 1 1 000 and a rubber tourniquet for the control of any general reaction that may occur As a tourniquet a two foot length of ⅜ inch soft rubber tubing is suitable

The tests may be performed on the arm or thigh in such a location that the tourniquet may be effectively applied above the highest tests if necessary The most uniform results are obtained on the anterolateral aspect of the upper arm or the anterior aspect of the thigh The skin of the forearm is less uniform the reaction to the same allergen varying somewhat in size according to the location of the test on the radial or ulnar aspects

In order to avoid mistakes in reading the tests it is best to follow a regular routine arrangement such as always starting at the upper medial location and placing the tests at uniform intervals of an inch or more in straight rows each of which is placed lateral to the previous one If the tests are listed on the records in corresponding columns it is easy to identify each test both at the regular time of reading and later if one of the tests shows a delayed reaction

Just before each row of tests is done the skin is cleaned with alcohol or a suitable nonstaining antiseptic solution In order to make the injection superficial the arm or thigh is grasped with the left hand so that the skin is held taut and gently stretched The needle is inserted almost parallel to the surface of the tense skin just far enough so that the bevel is covered and 0 01 to 0 02 ml of solution injected If the depth of the injection is suitable this produces a distinct 2 to 3 mm bleb or wheal in the skin which disappears in a few minutes unless a reaction occurs Failure to raise such a wheal indicates that the injection has been given too deep and the results will be less definite The beginner should actually measure the volume of solution injected and note if any is lost by leakage along the needle path As experience is acquired the *injection of a suitable volume may be adequately judged from the size of the* wheal produced With the intracutaneous test a control test is rarely necessary but if none of the tests done are clearly negative one may be done subsequently with the diluting fluid

It is apparent that the satisfactory performance of intracutaneous tests on small children requires adequate cooperation or control of the child Careful performance of a moderate number of the most pertinent tests is preferable to a large number hastily and carelessly performed on an upset and struggling child If these essentials cannot be accomplished the method of passive transfer should be used

In order to avoid excessive reactions it is best to inject not more than six tests at a time After these have been observed for five or ten minutes another similar group may be done the total at one visit usually not exceeding ten or twelve in older children or six to eight in small children

Grading the Results of Intracutaneous Tests—The reaction to an intracutaneous test is usually most marked after ten to fifteen minutes The reading of results should represent the greatest reaction observed rather than that noted at an arbitrarily set time interval There is no uniform method of recording the degree of reactions to intracutaneous tests Because of unavoidable variations in the amount of antigen injected and the depth of injection repetition of tests on the same patient shows some variations in the actual size of the wheal and erythema so that only a rough grading of reactions is worth while This is based primarily on the size of the wheal and the presence or absence of pseudopods or irregular extensions of the margins of the wheal The extent and intensity of erythema may influence the classification in borderline cases For the purposes of this book a well defined wheal 4 to 8 mm in diameter without pseudopods is classed as a slight or one plus reaction Rounded wheals 8 to 12 mm in diameter are classed as moderate or two plus reactions Reactions with wheals of 10 to 20 mm and pseudopod formation are classed as marked or three plus Larger reactions are read as marked active or four plus (Plate II C frontispiece)

While the recording of intermediate degrees of reaction may be useful on occasion these four classifications represent approximately the accuracy with which the reaction may be reproduced when the test is repeated and therefore form a practical scale In general the use of an allergen extract ten times as strong will produce a reaction of the next higher grade Thus a child showing a slight or one plus reaction to an extract of ragweed pollen containing 10 P N units per milliliter will *usually* show a moderate or two plus reaction to the 100 unit dilution and a marked or three plus reaction to the 1 000 unit dilution However considerable individual variations will be noted and in retesting with stronger extracts it is safest not to increase by more than tenfold at a time

As will be apparent from later discussions the intracutaneous test gives only a rough indication of the degree of sensitization In attempting to make such an estimate more information may be obtained from a series of tests with successive *tenfold dilutions of the same antigen than from a single test If the initial* test with an extract containing 100 P N units per milliliter gives a moderate or two plus reaction tests with 10 unit and 1 000 unit extracts will help to complete the picture if the 100 unit extract produces a marked or three plus reaction subsequent tests are done with 1 unit and 10 unit dilutions The degree of allergy may be expressed by the weakest dilution producing a marked or three plus reaction Slight reactions which are not accompanied by more definite reactions to stronger extracts of the same antigen are usually of doubtful significance If a reaction with pseudopods is obtained no stronger extract of the same allergen should be used because of the danger of producing a general reaction

Nonallergic Factors Affecting Skin Tests

Antiallergenic Drugs —The urticarial and erythematous reaction observed in the skin test depends not only upon the reaction of antigen and antibody but also on the subsequent release of histamine and the physiologic response to it These reactions are notably affected by many of the antiallergenic drugs Full doses of epinephrine ephedrine or the antihistamine drugs may practically inhibit the skin reactions The effect of aminophylline is less marked To insure satisfactory results skin tests should not be done within eight hours after the administration of these drugs Cortisone corticotropin and related steroid hormones have no apparent effect on skin reactions

Provided the above drugs are not being used it makes little difference whether the skin tests are done during a period of active symptoms or a free interval

Skin Reactions in Infants —The reactions of the skin of infants to tests by either the scratch or the intracutaneous method tend to be smaller than those seen in older children or adults of similar clinical sensitivity Some larger reactions with pseudopods may be noted but a large proportion of the apparently significant reactions are one plus or two plus by the standards given above Due allowance for this difference must be made in evaluating the reactions to direct skin tests on infants

The difference is apparently due to the texture and physiologic reactivity of infantile skin rather than immunologic factors The reaction of the skin of the infant to histamine is correspondingly reduced Carey and Gay have shown that if the skins of a normal infant and of a normal adult are passively sensitized with the same serums the reaction to testing with the same antigen is larger in the adult than in the infant

A similar difference between the infant and the older child or adult is noted when the sizes of reactions to direct skin tests and those obtained by passive transfer tests are compared If direct skin tests are done on an allergic infant and the same antigens are tested on the skin of a normal adult which has been passively sensitized with the infant's serum the reactions obtained by the passive transfer method are generally larger than those obtained by direct tests If the allergic patient is an older child or an adult the direct tests tend to give larger reactions than the passive transfer

When a number of skin tests on an infant are needed it is generally preferable to carry them out by the method of passive transfer both because of the more definite reactions and as a matter of convenience

Intracutaneous Tests With Bacterial Antigens

As previously mentioned many atopic diseases are obviously influenced by the presence of infections in the body and in certain instances seem to result from specific sensitization to the infective agents chiefly bacteria This type of bacterial allergy is different in its nature and manifestations from the delayed type of bacterial allergy typified by the tuberculin reaction discussed in Chapter 19

From analogy to the skin reactions produced by other allergens in atopic disease it might be expected that this type of bacterial allergy would be manifested by a typical immediate urticarial skin reaction Many attempts have been made to demonstrate such reactions by intracutaneous tests with vaccines filtrates and other antigens derived from bacteria In general these methods have failed to produce the desired results Immediate wheal reactions are only rarely elicited by bacterial antigens and in those cases where they occur they have *not been proved to be indicative of atopic sensitization to the bacteria* Delayed inflammatory reactions to intracutaneous tests with bacterial antigens are manifestations of the tuberculin type of bacterial allergy and presumably denote past or present infection by the organism but are unrelated to the occurrence of asthma or other atopic diseases

Such skin tests with bacterial antigens may give evidence of bacterial sensitization as a factor in asthma or urticaria when a general reaction with exacerbation of the symptoms of the disease follows the test This is not infrequently noted when such patients are skin tested with vaccines prepared from cultures of their sputum or nasopharyngeal secretions This type of general reaction may last several days and intentional production of it is not warranted as a routine diagnostic procedure Since such general reactions are not necessarily accompanied by a significant local reaction to the test it is apparent that little is learned from the local reactions to skin tests with bacterial antigens in these diseases Evaluation of the significance of the factor of infection must be based on other clinical evidence

PASSIVE TRANSFER TESTS

From the previous discussions of the Prausnitz Kustner phenomenon and the skin sensitizing antibody it is apparent that the skin of a normal person which has been passively sensitized by intracutaneous injection of the serum of an atopic patient reacts to tests with allergens similarly to the skin of the patient himself This permits the performance of diagnostic skin tests on the skin of a healthy substitute rather than the patient when direct tests are difficult or impossible It is useful (1) for testing infants and young children particularly if a considerable number of tests are necessary (2) when the skin of the patient is not suitable for tests because of *generalized eczema marked dermatographia* impetigo or other skin diseases (3) in cases of persistent severe allergic disease requiring frequent administration of epinephrine or antihistamine drugs which inhibit direct skin tests (4) in testing with antigens to which an extreme degree of sensitization is suspected so direct tests are considered dangerous and (5) as a further study of patients who react to an unusual number of antigens on direct tests so that the significance of the reactions is doubted

The reaction in the passively sensitized skin is strictly specific so that the results obtained by direct testing and passive transfer are essentially identical As in direct tests the size of reactions obtained by passive transfer varies somewhat with the physiologic activity of the skin the same sample of serum producing larger reactions in some individuals than others Since the skin of infants

usually reacts rather poorly to skin tests the reactions obtained by passive sensitization of the skin of a healthy adult with the serum of an infant are usually larger than those obtained in direct tests

The sensitization is strictly localized to the site where the serum is injected This necessitates care in testing at exactly the same point It also permits the performance of control tests on other areas of the skin with the antigens which produce reactions in the sensitized sites Because of the localization of sensitization there is no risk of a constitutional reaction from passive transfer tests Antigens may be used in somewhat stronger solutions than those ordinarily employed in direct intracutaneous tests The passive transfer tests may be safely done on the back of the test subject affording ample space and forty or fifty tests may be made at one sitting

While the sensitizing antibody remains fixed at the sites of injections antigens spread in the body and if sufficient amounts are present may elicit reactions in distant passively sensitized sites For example if sites in the skin of the back have been sensitized with serum sensitive to ragweed pollen injection of a large dose of ragweed pollen extract such as 10 000 or 20 000 units into the arm may elicit a reaction in all the sites This phenomenon does not afford a practical means of testing since ordinarily several different antigens must be tested in different sensitized sites However it may be important in two ways

(1) When several sites have been sensitized with a serum extremely reactive to a certain antigen testing one of them with antigen of the routine strength may occasionally induce a reaction in all the other sites Such a general flare up of all the sensitized sites is readily apparent and should not lead to misinterpretation but necessitates the repetition of the passive transfer tests on another subject When there is reason to suspect such an extreme sensitivity it is well to perform and record the tests with all the other allergens before testing with the suspected allergen

(2) If the serum used to sensitize the sites is highly reactive to a food allergen such as eggs peanuts or mustard eating of this food by the test subject may produce a reaction in all the sites When extreme allergy to such a food is suspected the test subject should be warned to avoid this food for several hours before the serum is injected and thereafter until the testing is complete

The passive sensitization of the site is well established after 24 to 48 hours and persists for several weeks The tests are ordinarily carried out two to four days after sensitization because of the difficulty of keeping the locations of the sites well marked for longer periods The persistence of sensitization is chiefly important when it is desired to use the same volunteer for several sets of tests An interval of at least two months should be allowed before the same area of skin is again used to avoid confusion which might be caused by persistence of the previous passive sensitization

Once a passively sensitized site has reacted strongly to test with an antigen subsequent tests of the site with the same antigen produce little or no reaction To a less marked degree the reactions to other unrelated antigens are also inhibited For reliable results a site which has once reacted should not be used again for diagnostic tests This applies also to sites which have flared up as a

result to injection of antigen into another site or as a result of ingesting a food to which the serum is reactive Sites which have been tested but showed no reaction may be retested with other antigens after 24 or 48 hours

The procedure of passive transfer tests obviously entails the possibility of transmission of infectious disease from the patient to the test subject The danger is greatest in the case of virus diseases particularly infectious hepatitis The method should not be used with the serum of patients recently recovered from any virus disease or those with a past history of hepatitis Bacterial infections may be excluded by Seitz filtration of the serum and by culturing it to prove sterility Syphilis may be excluded by suitable serologic tests

The test subject may be any healthy nonallergic adult whose skin is normal and not too deeply pigmented Blood type is not important One of the parents is a natural choice if known not to be allergic Any unsuspected allergies of the test subject are revealed by the control tests They do not cause error in the results but render the tests of no value in regard to the allergens involved Since the occurrence of many such reactions may necessitate repeating the procedure it is well to test the prospective test subject with a few common allergens before injecting the serum sites

Preparation of the Serum —Blood is drawn from the patient with a sterile dry syringe For a series of 30 to 40 tests 10 to 15 cc should be obtained The serum may be separated by centrifugation or by transferring the blood to a dry sterile flat bottle of about 500 cc capacity which is placed on its side until the blood clots then turned upright for several hours while the serum drains to the bottom The serum is then pipetted off to a sterile rubber capped vial Care should be taken to maintain sterility and avoid hemolysis The serum is tested for sterility by adding 0 3 cc to a broth culture medium and another sample used for a Mazzini or other serologic test for syphilis Sera which are contaminated with bacteria may be recovered by passing through a Seitz filter and retesting sterility Serum slightly tinged with hemoglobin is satisfactory that which shows marked hemolysis may cause irritation of the skin and give poor results Sterile sera stored at refrigerator temperatures retain their sensitizing activity for several years

Sensitization of Skin Sites —Passive transfer tests are usually done on the back of the test subject the arm or thigh is suitable if the number of sites to be used is small Each site is prepared by injecting 0 1 cc of serum intracutaneously superficially enough to raise a distinct wheal If the amount of serum available is small 0 05 cc for each site is adequate The sites are best spread about 1 5 inches apart so that 6 rows each of 7 or 8 sites can usually be made if desired The skin over the spine in the extreme flanks and at the base of the neck is somewhat less reactive and should be avoided The location of each site is marked with gentian violet solution a moistened indelible pencil or ink Four dots around the margin of the wheal suffice to indicate its extent The test subject should avoid washing the skin area during the period of the tests so that the marks will not be lost (Plate I *A* frontispiece)

The intracutaneous injections of serum often cause considerable erythematous reaction about the wheals produced This subsides in a few hours and does not interfere with the procedure

Testing the Sites —The tests may be made 2 to 4 days after the sensitization of the sites At that time the skin of the sites should be normal in appearance Sites which are inflamed after that interval usually indicate that the serum used was contaminated and cannot be expected to give reliable reactions

The sites are tested by the intracutaneous technique essentially as in direct tests The amount of antigen introduced may be somewhat greater since there is no risk of a constitutional reaction in the test subject It must be kept in mind that too large a dose of an antigen to which the serum is extremely reactive may spread to other sites and cause a flare up of all the sensitized areas destroying the value of the tests Such a reaction is rare if reasonable care is taken in choosing the antigen dilutions Pollens and inhalants may be tested in the 1 000 unit per milliliter strength and the foods in the same or stronger concentrations The volume injected for each test is usually 0 02 ml Care must be taken to make the test within the area where the serum was injected if the previous needle hole is still discernible the needle should again be inserted into it The reactions are read after 15 to 20 minutes on the same scale as direct intracutaneous tests (Plate I *B* and Plate II *D* frontispiece)

Control tests on an untreated area of the skin of the back or arm are done with all the antigens which react in the test sites If any of the control tests show significant reactions the corresponding reactions in the sensitized sites cannot be evaluated It is hazardous to attempt to judge the reaction of the serum by comparing the size of the test and control reactions If the reaction to the control test is slight and that in the sensitized site strong a clear cut result may often be obtained by repeating both test and control with a tenfold dilution of the antigen extract Otherwise the antigen involved should be tested in passive transfer on another test subject or in direct tests on the patient

Sensitized sites which have shown no reaction may be retested the following day with other antigens No attempt should be made to retest sites which have shown any reaction as the results will not be reliable

Results of Passive Transfer Tests —As previously indicated the reactions obtained on passive transfer are essentially the same as those of direct tests on the patient If the patient is an infant the reactions obtained by passive transfer are usually larger and more definite However allergens which are clearly negative on direct tests do not react on passive transfer On the other hand if the patient is an older child with a highly reactive skin some of the smaller reactions noted on direct tests may not be apparent in the passive transfer test Usually the reactions failing to transfer to normal skin are not clinically significant

While the reactions observed in passive transfer show a slightly higher degree of correlation than those of direct intracutaneous tests with the antigens actually proved to be important in causing clinical symptoms these results must also be evaluated in conjunction with the history and observations of the clinical course

SIGNIFICANCE OF SKIN TESTS

If the skin test is performed on a sensitive but physiologically normal skin a definite and reproducible skin reaction is valid evidence of allergy of the skin to the allergen or allergens contained in the extract Likewise a definite reaction in a passive transfer test with a negative control test indicates the presence of skin sensitizing antibody in the patient s serum Both types of reaction are evidence of the existence of the allergic constitution and thus may be helpful in the differentiation of allergic disease from other types of illness quite aside from the etiologic significance of the particular antigens The value of these tests in diagnosis of specific sensitization depends upon the degree to which the skin reaction or the presence of circulating antibody is correlated with the occurrence of actual symptoms of disease when the child is naturally exposed to the allergen

✓ In most of the common allergic diseases the correlation is sufficient to make direct or passive transfer skin tests practically indispensable evidence in arriving at a specific diagnosis However the correlation is not such that each positive skin or passive transfer reaction can be considered infallible proof that the child is clinically sensitive The reaction to skin or passive tests must be evaluated in conjunction with the history and the observed course of symptoms under various changes of environment or diet in arriving at the final diagnosis of sensitization

The correlation between reactions to skin tests and clinical sensitization varies in different forms of allergic disease being greater in hay fever and asthma than in eczema Also the correlation of reactions to skin tests with inhaled allergens to clinical symptoms tends to be greater than that of reactions to food allergens

Inhaled Antigens —The clinical significance of antigens giving positive skin reactions is most apparent in the case of pollens because of the seasonal nature of exposure In typical hay fever skin tests with extracts of the pollen causing symptoms usually give definite reactions and the serum contains skin sensitizing antibodies which react with the pollen extract in passive transfer However during the course of development of the disease the clinical skin and passive transfer reactions do not necessarily develop simultaneously and so discrepancies between them are frequently noted If a child of 3 or 4 years begins to show symptoms of rhinitis during the ragweed pollen season skin tests and passive transfer tests may remain negative for a year or more but gradually become positive as the disease develops over a period of two or three years On the other hand in testing children with eczema who have never had hay fever it is not unusual to find direct skin reactions or passive transfer reactions to ragweed pollen extract In the course of a few years a considerable proportion of children showing such reactions may be expected to develop clinical hay fever

The child with definite clinical allergy to ragweed pollen reacting to this antigen on skin tests or passive transfer will often also show skin reactions and passive transfer tests to extracts of grass or tree pollens which have not

been observed to affect the child clinically Occasionally these false positive reactions may equal or even exceed the reaction to ragweed in size In such cases only the diagnosis of ragweed hay fever is warranted since the clinical symptoms have been limited to that season However the reactions to grass and tree pollens may be important in later years This change may become apparent abruptly with a change of environmental exposure for example if the child who has previously lived in the city moves to the country where pollens are more abundant hay fever may occur during the tree and grass pollen seasons as well as during the ragweed season Even without a change of location tree or grass hay fever may occur during years when the concentration of these pollens are unusually heavy because of weather conditions

The skin test or the passive transfer reaction is only a rough index of the degree of clinical sensitization and it is essential to judge from the history and course of symptoms which of the antigens causing skin reactions are clinically significant One must remember however that the differentiation is not necessarily a sharp one The clinically insignificant reaction may well prove to be significant at a later date because of either further development of sensitization or of greater exposure to the antigen The actual distinction is between reactions which are important under present circumstances and those which are not

In the evaluation of nonseasonal environmental antigens judgment is more difficult than in the case of pollens If a child with perennial respiratory allergy shows positive skin reactions to several inhalant allergens with which he is in constant contact evaluation of the significance of each separate reaction is rarely possible In the presence of multiple sensitizations elimination of any one factor may not produce a definite change in symptoms The only logical procedure in such cases is to assume that all the inhalant antigens which give moderate or marked positive skin reactions and to which the child is exposed are important

Food Allergens —The evaluation of skin reactions to food allergens is more difficult than in the case of inhaled allergens Allergic children giving moderate (two plus) or even marked (three plus) reactions to foods may be found not infrequently to be able to eat these foods in ordinary quantities without any apparent symptoms On the other hand in rarer instances a child who is shown by repeated actual trials to develop symptoms from a particular food may show a completely negative reaction to a skin test with it

The relatively greater incidence of false positive skin reactions to foods than to inhaled allergens may be partially explained by the route of exposure When respiratory allergy results from inhalation of an antigen the particles of antigen come into direct contact with the sensitized tissues On the other hand food allergens are greatly altered by cooking digestion and metabolism before reaching the shock organ through the circulation While it is known that significant traces of some potent allergens such as egg and peanut are absorbed in an active form digestion (and in many cases cooking) produces sufficient chemical change to inactivate most antigens to a considerable degree This is evidenced in bakers asthma of adults Asthma due to inhalation of flour

is fairly frequent among workers in bakeries and is accompanied by a skin reaction to flour Most of these patients are able to eat bread freely without the occurrence of symptoms the skin reaction correlating with the clinical effects of inhalation but not those of ingestion

It is a familiar observation that allergic reactions to foods which occur within a few minutes to an hour after ingestion of the food are associated in a relatively high proportion of cases with positive reactions to skin tests while patients in whom the allergic reactions occur four to twelve or more hours after ingestion of the causative food are apt to show negative skin reactions to the food allergen To some extent this may be explained by the fact that the immediate reactions often result from an unusually high degree of general sensitization of which strong skin reactions are one manifestation However the occasional association of rather severe delayed clinical allergic reactions to food with a completely negative response to the skin test suggests that the delayed reaction may result from a different mechanism than the immediate reactions In a few carefully studied (adult) patients with such delayed food allergies Cooke has shown that skin tests with the causative food gave no reaction but that skin tests with proteoses derived from that food by artificial digestion in vitro gave positive reactions He suggested that these patients were allergic not to the original food as eaten but to antigenic substances liberated in the process of its digestion This observation appears to account for the false negative skin reactions observed in such delayed food allergies but the method of study has not been widely applied and the extent of its applicability remains undetermined

While the correlation of the immediate type of food allergy with the reactions to skin tests is relatively good some false negative skin reactions are also observed in this group particularly in patients allergic to berries and shellfish In most of these cases this discrepancy is due to the allergen extracts used for skin tests rather than the mechanism of sensitization Strawberries raspberries blackberries and the various edible shellfish contain antigens which are extremely unstable and rapidly lose their potency in the ordinary extracts prepared for skin tests even at refrigerator temperatures Patients allergic to these foods may give positive reactions to scratch tests with the fresh or quick frozen food although intracutaneous tests with all available prepared extracts of the material are negative This does not indicate that the prepared extracts are completely inert as other patients may show definite reactions to them but they cannot be relied upon to contain all the important antigens in the fresh material When the intracutaneous test fails to confirm a history of sensitization to one of these foods it should be supplemented by a scratch test with the actual food

MUCOSAL TESTS

In addition to skin tests the reactions of the mucosae of the eye nose and bronchi to contact with allergens have been used to detect sensitization Of these procedures only the *conjunctival test* or *eye test* has been developed to

a point where it may be considered as a routine procedure This consists of dropping the antigen either in a suitable solution or in a dry form such as actual pollen grains into the conjunctival sac A positive reaction consists of redness itching and in more severe cases of edema of the conjunctival membrane For comparison it is best to test only one eye leaving the other as a control Rubbing the eyes should be prevented during the test Uncomfortable reactions may be controlled by the use of epinephrine and cocaine eye drops (Chapter 1) after the response has been observed

While the conjunctival test is not limited to inhaled allergens and has been used as a test for sensitization to heterologous serum it is most often used for the detection of allergy to inhaled antigens particularly pollens Since the conjunctivae act as a shock organ in hay fever and to a less extent in other respiratory allergies the reaction of the conjunctivae is more closely related to the actual clinical sensitization than is the skin reaction In the case of children first developing hay fever where it has been noted that the appearance of the skin reaction may either precede or follow the first occurrence of clinical symptoms by a year or more the eye test may be expected to show more significant results than the skin test In the great majority of cases of established hay fever the conjunctival reaction parallels the skin test but is less sensitive than the intracutaneous test and more sensitive than the scratch test When the same allergen extracts are used for all three types of tests the lowest concentration producing the eye reaction is usually about ten times that required for the intracutaneous reaction but only one tenth that needed for a positive scratch test If the intracutaneous test has been performed with increasing concentrations of pollen extract up to a maximum of 5 000 to 10 000 P N units per milliliter few additional cases of sensitization will be detected by the eye test even using dry pollen However if the skin tests have been done by the scratch technique the eye test may reveal sensitization in a considerable number of additional cases The physician using the intracutaneous test routinely will have need for the eye test only in occasional cases where sensitization suggested by the history is not confirmed by the skin test

CORRELATION OF SKIN REACTIONS AND HISTORY

From the history the physician arrives at certain suspicions as to the causative factors affecting a child with allergic disease and also lists the potential allergens to which the child is exposed regardless of whether they have been noted to cause symptoms In the performance of skin tests care is taken to avoid the use in intracutaneous tests of too strong an extract of allergens to which the history directs suspicion If the sensitization to a particular antigen seems from the history to be unusually acute a scratch test with that antigen may be done before attempting intracutaneous tests If the sensitization is apparently less active the initial intracutaneous test may be done with an extract one tenth to one one hundredth the strength recommended for average cases If these initial tests give negative or slight reactions successive intracutaneous tests are done with tenfold increases of concentration until a two plus or three

plus reaction is obtained or until a concentration of 5 000 to 10 000 P N units is reached If the suspicion based on the history is confirmed by the skin tests there is no problem in arriving at a diagnosis

Among the other skin tests done are included all those allergens to which the history has indicated exposure which are considered potential factors in the disease being studied In the absence of special suspicion these are tested in the average recommended strengths If the skin reactions to these or other allergens are noted the history is reviewed after the completion of skin tests to consider whether these skin reactions reasonably explain the time and circumstances of occurrence of symptoms With the advantage of the knowledge gained from the skin reactions the interpretation of the history may be quite different from the impression gained before the tests were done

In the correlation of the history and the results of the skin tests one must remember that the degree of clinical sensitivity varies greatly in different patients A child extremely sensitive to a cat may have obvious asthma within 15 or 20 minutes every time he is exposed On the other hand a child with mild sensitization may have symptoms only intermittently despite constant exposure to a cat in the home The allergy in the latter case may be manifested by rhinitis apparent only on examination of the nose and perhaps a few sibilant rales heard on auscultation of the chest but with asthma clinically apparent only when precipitated by some secondary factor such as exertion chilling or respiratory infection Such mild sensitization is important to the health of the child as it not only renders him liable to attacks of asthma in periods of stress but also through the persistent allergic rhinitis makes him more susceptible to respiratory infections Obviously the extreme degrees of sensitization are easily brought out in the history the lesser degrees may only be inferred from a knowledge of their potential effects

As previously noted the evaluation of clinical sensitization to pollens is relatively easy because of the seasonal incidence of exposure The size of a skin reaction is not a definite criteria of its clinical significance The actual occurrence of hay fever depends on the intensity of exposure as well as the degree of the child s allergy The practical question in diagnosis is whether or not the pollen is causing symptoms under the conditions and activities of his life A one plus reaction confirmed by the history is more important than a three plus reaction which is not confirmed

Estimating the importance of each of a number of nonseasonal inhalant antigens to which the child is exposed most of the time may be impossible When respiratory allergy results from the combined effects of exposure to a number of nonseasonal allergens the effect of elimination or addition of one antigen may not appreciably alter the clinical picture This presents a problem when one of the antigens incriminated by skin tests is a pet dog or cat Both child and parents may be loath to accept the significance of the reactions to the pet particularly if the attacks also occurred before it was in the home or when the child was visiting in houses where there were no pets While it may be impossible to prove conclusively that the dog or cat reaction is important the only safe

course is to assume that it plays a part in causing the symptoms and eliminate contact

Because of the frequency of false positive reactions to food allergens reactions in this category must be evaluated with special care Children with asthma or allergic rhinitis often show positive skin reactions to foods but relatively few of these foods actually can be shown to induce symptoms when they are eaten Hill has estimated that only 20 to 25 per cent of such reactions are clinically significant It is important to recognize this fact so that the asthmatic child will not be needlessly deprived of good foods and kept to a restricted diet which is often poorly balanced in nutriments In allergic eczema also a large proportion of the skin reactions to foods prove to be of little etiologic significance

DIETARY TRIALS

The history may or may not be of value in confirming the skin reactions to foods The suspicions of the parents with regard to food allergy are often biased by previous advice based either on food tests or general principles and may prove quite erroneous Often various foods have been eliminated for indefinite periods without apparent change in the condition indicating that the foods eliminated were actually not of great importance When the history fails to supply satisfactory information dietary trials are essential before one arrives at the conclusion that foods are of real etiologic importance If the child shows two plus or stronger skin reactions to a few commonly eaten foods it is logical to exclude these suspected foods from the diet for a period of two weeks and observe the results If the change of diet produces a definite improvement in the symptoms it may be presumed that one or more of the suspected foods is an important factor in the etiology Which food is significant may be determined by restoring one of the group at a time to the diet at intervals of 4 to 7 days and watching for a return of symptoms Conclusive proof requires that the symptoms improve with elimination and return with the addition of the same food on three successive trials If the relationship is striking and the symptoms are severe one is justified in accepting a less rigorous proof

On the other hand if the elimination of the foods showing positive reactions does not produce relief it is apparent that these are not the chief causative agents although they may be minor contributory factors in a condition due primarily to inhaled allergens or infection This type of procedure obviously does not throw light on the relatively rare cases in which the patient is sensitive to a food which gives negative skin reaction

More elaborate dietary programs which do not depend on the reactions to skin tests but may serve to confirm them are *elimination diets* and the *food diary* Both of these methods require several weeks of study and are warranted only when there is a strong suspicion of food allergy which is not elucidated by the skin tests Elimination diets are suitable for cases in which symptoms occur almost daily the food diary for diseases characterized by periodic attacks occurring at intervals of several days or more

The elimination diet aims to exclude the foods believed to cause allergic disease most commonly such as milk eggs chocolate and wheat or all grain products In the case of infants a soybean preparation is substituted for milk In adapting this general program to the individual patient any other foods suspected on the basis of the history or skin tests are also excluded If any of the foods eliminated are important causative factors improvement should be apparent within a week The particular food involved is then determined by adding one at a time as in the case of eliminations based on skin reactions If this type of diet does not produce relief in older children one may try a more severely restricted diet consisting only of a few foods which statistically are rare causes of allergy such as lamb rice peas and pears for a period of one week When any such diet is advised no other important changes in treatment should be made at the same time to avoid misinterpretation In evaluating the results thought should also be given to the possible influence of inhaled allergens respiratory infections and nonspecific contributory factors

The *food diary* consists of a daily record of all foods eaten at each meal and between meals and of the time of occurrence of symptoms After two or three attacks have occurred an attempt is made to correlate the symptoms with the foods eaten in the twelve to twenty four hours preceding each attack The diet is usually unrestricted since the success of the method depends upon the recurrence of symptoms If one or two foods are suspected after the first few attacks they may be eliminated and the subsequent course observed If no attack has occurred after two or three times the usual interval they may be restored to the diet one at a time to see whether an attack is induced

Recurrence When Causative Food Is Added—The practicing physician is properly more concerned with relieving his patients than establishing scientific facts For this reason he may be inclined to rest on his laurels when he finally arrives at a diet which does not cause symptoms However it should be understood that improvement of symptoms may be due to the natural course of the disease or to other therapy given as well as the dietary changes Actual proof that a food is the cause of symptoms requires that the condition be consistently reproduced twice or three times by restoring the suspected food to the diet If a considerable number of important foods have been eliminated such proof of the really significant factors is of interest to the patient so that he will not be left indefinitely on a needlessly restricted diet It is always important if the physician wishes to cite the patient to his colleagues as an example of food allergy A tremendous amount of confusion and contradiction in the medical literature results from failures to distinguish between a temporal relationship of treatment and result and a true cause and effect relationship

ENVIRONMENTAL TESTS

In the case of children with multiple skin reactions to inhaled allergens and also evidence of infection it is often difficult to evaluate the relative importance of extrinsic allergens and infection in producing allergic symptoms particularly asthma This problem is usually most quickly resolved by removing the

child from his home environment to the relatively dust free hospital The hospital bed should be free of feather pillows and if the test is performed during the pollen or mold spore seasons the windows should be equipped with suitable filters Single doses of suitable medications may be given as necessary for the relief of symptoms but the routine administration of medicines to prevent symptoms is avoided so that any improvement in symptoms may be related to the environment rather than drugs If the symptoms are due to inhaled allergens marked relief is expected within four days Symptoms persisting after this period may be due to infection or foods The factor of infection can be evaluated by a trial of suitable antibiotics and the food factor if necessary by dietary restrictions If emotional stress in relations with parents has been suspected as a factor observation of the child during and after visiting hours may be helpful

GENERAL PRINCIPLES

The variety of different methods used in diagnosing the specific causes of allergic disease reflect not only the many types of factors which may be important but also the fact that no one approach can be relied upon in every case While skin tests play an important part in such diagnosis undue emphasis and reliance upon them may lead to serious errors Probably the most common mistakes are made in overlooking infective factors and in attaching unwarranted significance to skin reactions to food tests without confirmation by clinical trial In subsequent chapters dealing with the various diseases an attempt is made to indicate the relative importance of infection inhaled allergens and foods in each

The final etiologic diagnosis must be based on judgment in assembling information from the various diagnostic approaches not simply a summary of skin reactions It must adequately account for the occurrence of symptoms under the observed circumstances if it is to serve as the basis for successful treatment Common sense in evaluating the whole picture is more often important than brilliance in suspecting an obscure and exotic allergen

This book is intended to help the practitioner in handling the allergic diseases of his pediatric patients and not to qualify him as a specialist in allergic diseases However as his interest ability and physical equipment for studying and treating these conditions become known it is possible that other physicians in the area may ask his aid in handling their allergic patients Many of these patients will be sent to him for skin testing with the implication that the referring physician will handle the other aspects of diagnosis and treatment The exact division of labor between the referring physician and the consultant will depend on the two physicians and on local custom but it should be understood that the interpretation and evaluation of the results of skin tests require more specialized ability and judgment than performing them If the allergist simply carries out a routine series of tests and reports the readings he is acting as a technician rather than a physician and must expect his colleagues to regard him as such On the other hand if he makes an adequate study of each

The elimination diet aims to exclude the foods believed to cause allergic disease most commonly such as milk eggs chocolate and wheat or all grain products In the case of infants a soybean preparation is substituted for milk In adapting this general program to the individual patient any other foods suspected on the basis of the history or skin tests are also excluded If any of the foods eliminated are important causative factors improvement should be apparent within a week The particular food involved is then determined by adding one at a time as in the case of eliminations based on skin reactions If this type of diet does not produce relief in older children one may try a more severely restricted diet consisting only of a few foods which statistically are rare causes of allergy such as lamb rice peas and pears for a period of one week When any such diet is advised no other important changes in treatment should be made at the same time to avoid misinterpretation In evaluating the results thought should also be given to the possible influence of inhaled allergens respiratory infections and nonspecific contributory factors

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Chapter 10

INJECTION TREATMENT

General Principles

The possibility of increasing the tolerance of an atopically sensitized patient for the causative allergen by a suitable series of injections of the specific allergen has been discussed in Chapter 7 As pointed out there such treatment does not depend on decreasing the amount of sensitizing antibody present and leads to the development of a blocking antibody so that it is more exactly described as immunization than desensitization

Since the material injected is the antigen causing symptoms and the development of tolerance depends upon the reaction of the patient s body to it the amount injected must be small enough not to produce an undue reaction yet large enough to produce an adequate stimulus for immunization The first dose must be carefully adjusted to the degree of sensitization of the individual patient and subsequent doses cautiously increased as development of tolerance permits This gradual increase of dosage is continued until a dose is reached which is believed to be adequate for the relief of symptoms but still well tolerated by the patient The actual top dose varies widely in different cases Some idea of the adequate dose may be gained from the degree of sensitivity indicated by skin tests but the accuracy of such an estimate becomes apparent only as treatment is carried out The magnitude of the increase of tolerance is indicated by the fact that the top dose is not infrequently 500 to 1 000 times the first dose

During the period of building up the dosage the injections are given once or twice a week Attempts to hasten the treatment by giving injections more often than every three days is likely to cause reactions which apparently result from failure of the body to completely eliminate one dose before another is given When a suitable top dose is reached it is repeated at intervals of two

to four weeks to maintain protection In general tolerance begins to decrease about a month after the last injection therefore this is the longest interval at which the same maintenance dose can be safely repeated

During periods of heavy exposure to the antigen as at the height of the pollen season increasing doses of antigen are not as well tolerated as at other seasons of the year For this reason treatment with pollens should be started if possible early enough to allow reaching the full dose before the onset of the pollen season This program is spoken of as *preseasonal treatment* If injection treatment with pollen extract is started at the height of the pollen season *(co seasonal treatment)* a far more cautious program of dosage is needed than at other times of the year Treatment with nonseasonal allergens is of necessity usually carried out in the face of moderate exposure to antigen but if care is taken in progressing the dosage tolerance can generally be developed satisfac torily

Indication for Injection Treatment

When allergic disease is caused by antigens which can be avoided the relief of symptoms by elimination of contact is usually far quicker and more certain than that produced by attempts to increase the tolerance of the patient Injec tion treatment is indicated in those cases where satisfactory avoidance of the antigen is difficult or impossible The antigens most often used in desensitiza tion are pollens mold spores and house dust since it is in general impossible to avoid these allergens sufficiently by reasonable measures The use of many other inhalant antigens may be indicated by the circumstances in particular cases In jection treatment with food antigens is rarely indicated and the results are gen erally unsatisfactory In bacterial allergy vaccines and filtrates are frequently employed for injection treatment when the infection cannot be eliminated by antibiotics or surgical procedures

Results

The results obtained by injection treatment will obviously depend on the accuracy of the etiologic diagnosis as the treatment must include all the im portant factors which are not being avoided From the practical standpoint however results are usually better if attention is focused on a relatively few really significant causes rather than diffused to include a multitude of antigens giving slight skin reactions but not definitely known to be of clinical importance For example many children with hay fever react to skin tests with a large num ber of pollens but are best treated only with those to which there is known ex posure and during the seasons of which symptoms occur The other reactions may indicate potential or future clinical sensitizations but the essential point of the treatment is to correct the conditions presently causing symptoms Attempts to treat with too many antigens often result in giving inadequate doses of the most important

In cases of hay fever or asthma due to a single pollen suitable injection treat ment may be expected to produce marked relief of symptoms in 75 to 80 per cent

of patients Some of these patients are practically free of symptoms others have mild symptoms on a few days of heavy pollination but these can usually be readily controlled by occasional doses of symptomatic medications When the allergic disease is due to a multitude of different allergens the results of injection treatment are less favorable The presence of respiratory infection as a complication also adversely affects the results of injection treatment

Technique and Necessary Precautions

Even in the best hands uncomfortable and sometimes dangerous constitutional reactions will occasionally follow injection treatment and one must always be prepared for this emergency Epinephrine 1 1 000 for injection and a rubber tourniquet should be at hand before giving the injection It is recommended that the injections be given by the physician himself If this duty is delegated to a nurse injections should only be given when the doctor is immediately available if a reaction occurs

The reaction to the previous injection and the time elapsed since it are noted since there are factors determining the dose to be given as explained below The dose is accurately measured in a 1 ml tuberculin or allergy type syringe with care being taken to expel air bubbles which would cause an under dose and hence a disproportionate increase when the next scheduled dose is given in full at the following visit The injections are given on the outer surface of the upper arm or thigh in such a position that the tourniquet may be securely applied above the site in case of an excessive reaction The skin surface is cleaned with alcohol or Zephiran A short (¼ inch) 26 gauge needle is used and the antigen injected subcutaneously care being taken to avoid visible veins If two injections are given it is well to place one on each arm or thigh so that the local reactions to each may be noted separately

After the injection the patient is kept waiting in the office for twenty to thirty minutes to observe the local reaction and watch for signs of a constitutional reaction Constitutional reactions may begin after a longer interval but the severe and dangerous ones are almost always apparent by this time

DOSAGE

The doses of antigen used in injection treatment are of paramount importance in determining the results obtained These must be carefully adjusted to the degree of sensitivity of the individual patient and his ability to develop tolerance as the treatment progresses These factors vary so much in different patients that age and body weight are of negligible importance by comparison The doses given children of 6 or more years of age are essentially comparable to those given adults In infants and younger children the doses may be kept somewhat lower at the start but may be increased gradually to essentially the same doses if well tolerated

Because of the marked variations in the doses given individual patients there is no unanimity among allergists as to what is a suitable dosage range for the majority of patients of an average degree of sensitivity It is the belief

of the authors that this wide divergence of opinion as to what constitutes adequate treatment is largely responsible for the variations in results obtained by different physicians using this form of treatment. *Many authorities on the* subject habitually use doses considerably lower than those suggested in the subsequent tables. No doubt many children might experience satisfactory results with either lower or higher doses. The benefits are not proportional to the doses reached. Doses beyond the tolerance of the patient obviously cause reactions and unsatisfactory results. However, it is felt that within the limits of tolerance relatively large doses produce a higher percentage of good results *and in continuous maintenance* treatment over a period of years more instances in which the reactivity decreases to a point which permits termination of treatment.

The beginner in this field of medicine obviously needs some guide as to the doses to be used, and for this reason typical schedules are given below. However, it is essential to realize that development of tolerance in different patients will vary so widely that any projected schedule must be constantly varied according to the reaction of the patient.

Titration of the degree of sensitivity by intracutaneous tests with various dilutions of the antigen gives valuable information as to a safe initial dose and at *least a rough idea of a reasonable progression of subsequent doses. The patient* is tested successively with approximately 0.01 ml. of dilutions of antigen containing 10, 100 and, if necessary, 1,000 protein nitrogen units per milliter until a three plus reaction is obtained. The reaction to each dilution is observed before progressing to the next stronger. The degree of sensitivity is determined by the weakest dilution producing a three plus reaction with classification as follows:

3 plus reaction to 10 unit dilution	Class A	Highly sensitive
3 plus reaction to 100 unit dilution	Class B	Average sensitivity
3 plus reaction to 1,000 unit dilution	Class C	Moderate sensitivity
2 plus reaction to 1,000 unit dilution	Class D	Relatively insensitive

On the basis of this classification, the accompanying schedules are suggested as a guide in preseasonal treatment with pollens and treatment with nonseasonal inhalants (Table XIII). Doses are given once or twice a week at intervals of at least three days.

While the doses in Table XIII are stated in protein nitrogen units, the same general progression can be used for pollen units or total nitrogen units if the patient has been classified with the same extract used for treatment.

These schedules represent the progression of dosage and top doses *usually* safe in patients of each class. They do not necessarily indicate the fastest increases or highest doses that will be tolerated, but the inexperienced worker will do well to consider them as the maximum increases to be made if there is no undue reaction to the injections.

The dosage schedule must be modified in accordance with the local reactions to the injections. Usually the injection will produce a slight swelling and *an area of redness about 2 cm.* in diameter appearing within 20 minutes and lasting several hours. After a reaction of this or lesser degree one may safely proceed according to the schedule. If any injection produces a large

TABLE XIII

DOSAGE IN PROTEIN NITROGEN UNITS FOR NONSEASONAL ALLERGENS AND FOR PRESEASONAL TREATMENT WITH POLLENS

DOSE	CLASS A	CLASS B	CLASS C	CLASS D
1	1	5	20	40
2	2	10	40	80
3	4	20	80	150
4	7	35	140	250
5	10	50	200	400
6	15	70	300	600
7	0	100	400	900
8	30	150	600	1 400
9	40	00	800	2 000
10	60	300	1 000	3 000
11	90	400	1,500	4 000
12	120	600	2 000	5 000
13	150	800	3 000	6 000
14	200	1 000	4 000	8 000
15	250	1 500	5 000	10 000
16	300	000	6 000	12 000
17	350	2 500		

Doses given once or twice a week

swelling persisting more than thirty six hours but no constitutional symptoms the same dose is repeated at the following visit Usually this repetition allows a chance for increase of tolerance so that the local reaction is less the second time but the question of further increase is again decided on the same principles Local reactions intermediate in degree between the slight reaction permitting the normal increase and the large reaction which contraindicates any increase call for a smaller increase than that specified in the schedule the exact amount depending on size and duration of the reaction The persistent occurrence of excessive local reactions may require changing the patient to a schedule for a more sensitive class

The occurrence of any constitutional reaction necessitates dropping back two doses from the one causing the reaction and then proceeding on a more cautious schedule If a second general reaction occurs at the same dosage level this should be considered the limit of tolerance of the patient and subsequent treatment confined to lower doses

The schedules are planned for injections given once or twice a week with a minimum of three days between doses If the treatment is interrupted the doses require adjustment If the interval between doses is not over two weeks the normal increase in dosage may safely be made If the interval is three or four weeks the previous dose may be repeated but not increased Intervals of five to six weeks require a reduction to two thirds of the previous dose of two months to one half

Since house dust extracts are rarely standardized in units the schedules in Table XIII are not applicable For the ordinary dust extract supplied in concentrated form 1 10 and 1 100 dilutions the schedules given in Table XIV may be used This is not suitable for highly concentrated preparations of dust allergen such as Endo dust

TABLE XIV

DOSAGE FOR DUST EXTRACTS

DOSE*	PATIENTS WITH 3 PLUS REACTION TO DUST 1:10		PATIENTS WITH 3 PLUS REACTION TO DUST CONCENTRATED	
1	Dust 1:100	give 0.2 ml	Dust 1:10	give 0.2 ml
2	1:100	give 0.4 ml	1:10	give 0.4 ml
3	1:100	give 0.7 ml	1:10	give 0.7 ml
4	1:10	give 0.1 ml	concentrated	give 0.1 ml
5	1:10	give 0.2 ml	concentrated	give 0.15 ml
6	1:10	give 0.3 ml	concentrated	give 0.2 ml
7	1:10	give 0.5 ml	concentrated	give 0.3 ml
8	1:10	give 0.7 ml	concentrated	give 0.4 ml
9	concentrated	give 0.1 ml	concentrated	give 0.5 ml
10	concentrated	give 0.15 ml	concentrated	give 0.6 ml
11	concentrated	give 0.[illegible] ml	concentrated	give 0.7 ml
12	concentrated	give 0.3 ml		

*Doses given once or twice a week

If treatment with pollens is started during the season (coseasonal) a far more conservative dosage than that suggested in Table XIII must be used. The schedules indicated in Table XV are more suitable.

TABLE XV

DOSAGE FOR COSEASONAL TREATMENT WITH POLLENS (PROTEIN NITROGEN UNITS)

DOSE	CLASS A	CLASS B	CLASS C	CLASS D
1	1	2	10	10
2	2	4	15	15
3	3	7	20	20
4	5	10	25	30
5	7	15	30	40
6	10	20	35	50
7	15	25	40	60
8	15	30	50	80

Doses in Table XV are given every two or three days and the top dose repeated at the same intervals until symptoms subside. At the end of the pollen season a change may be made to the schedules given in Table XIII or treatment may be dropped and preseasonal treatment given the following year.

Maintenance Treatment

When the patient has reached a satisfactory dose and the symptoms are controlled the same dose is repeated for maintenance treatment. The frequency of the injections at this stage depends on the degree of exposure to the antigen. If the maintenance dose of a pollen is reached immediately before the season one may repeat the dose weekly through the pollen season if there is no excessive reaction. If this dose produces a marked local reaction or any suggestion of a general reaction it should be reduced by one half during the season of heavy pollen exposure. At the end of the season the same dose may be

continued at intervals of three to four weeks In the case of nonseasonal antigens the maintenance dose is at first given every two weeks If symptoms are well controlled the interval between injections may be increased to three and later to four weeks The interval of four weeks is the longest at which the same dose can be safely repeated and so represents the maximum interval for maintenance treatment On the other hand if symptoms recur when the change is made from weekly doses to a maintenance dose every two weeks the interval may be reduced again to one week the size of each dose remaining the same

Most of the allergen extracts used for injection treatment undergo a considerable loss of potency over a period of one year even if constantly refrigerated It is therefore necessary to change to fresh extracts at least once a year When this is done one must allow for the difference in potency of the old and new extracts in adjusting the dose of patients on maintenance treatment In general the first dose of the fresh extract is one third to one half the last dose of the old extract Subsequent doses are increased in accordance with schedules in Table XIII giving the injections at intervals of not more than two weeks

When a child is receiving maintenance treatment it is helpful to repeat the skin tests with the antigens used in treatment once a year In many patients the results of whose treatment have been perfectly satisfactory the degree of sensitivity as indicated by the skin test remains the same from year to year In others there is a significant decrease in the skin reaction placing the patient in a less sensitive class When such a change occurs if there have been no undue reactions to the injections during the previous year it is advisable to progress the dosage to that suggested for the new classification This increased dosage offers the hope of more complete control of symptoms and also of a further decrease in the degree of sensitivity When the symptoms have been completely controlled for a year or more and the reaction to the skin test is so reduced that the 1 000 units per milliliter dilution gives little or no reaction one may consider discontinuing treatment with that antigen After the treatment is stopped under these conditions some patients remain free of symptoms indefinitely while others experience a gradual return of symptoms after a period of months or years The recurrence is usually gradual and treatment can be renewed before the symptoms become serious so that no great risk is involved

CONSTITUTIONAL REACTIONS

The chief difficulty in injection treatment is the possibility of constitutional reactions The symptoms and treatment of such reactions have been described in Chapter 7 Our concern here is with the means of avoiding their occurrence in so far as possible It must be recognized however that if a large number of patients are given adequate treatment some reactions will be encountered The reasons for constitutional reactions to injections may be listed as follows (1) too large an initial dose (2) too rapid an increase of dosage (3) reaching the limit of tolerance for the patient (4) simultaneous heavy exposure to inhaled pollen (5) too long an interval between injections (6) change from one prepara

tion of extract to another (7) error in dosage (8) accidental injection into a vein and (9) unusual exertion shortly after the injection

If the patients are classified as to degree of sensitivity by intracutaneous tests as described there is relatively little danger that the first dose suggested for that class will produce a constitutional reaction It represents only a reasonable increase over the amount of antigen that has been injected in the skin test However if the skin test has caused an unduly large and prolonged local reaction treatment may well be started with one half or one quarter of the specified first dose

The doses suggested for subsequent treatment are those that are easily tolerated by the great majority of patients in each class However as previously stated individual patients develop tolerance at different rates The local reaction noted after each injection is the best guide to the patient s tolerance As a rule when the schedules are followed large and persistent local reactions to one or two injections precede a constitutional reaction which is due purely to *too rapid an increase of dose If the subsequent dose is modified when an excessive* local reaction is noted many constitutional reactions from this cause may be avoided

Certain patients have a fixed limit to their tolerance for antigen called a ceiling dose which cannot be exceeded without a constitutional reaction The top dose suggested for each class of patients is below the ceiling dose of the great majority of patients in that class but there are occasional exceptions whose limit of tolerance is considerably below the suggested top doses for their class When a constitutional reaction occurs at moderate dosage it is impossible to be sure whether or not the patient may eventually progress to higher doses However if the dose is reduced and then brought up by smaller increments and a second general reaction occurs at approximately the same level of dosage this dose may be presumed to represent the patient s ceiling The dosage is then kept below this limit for at least several months or a year

The effects of simultaneous heavy exposure to inhaled antigen are most *often apparent at the peak of the pollen season At this time no increase should* be made in the dose of pollen injected and if the symptoms seem to be worse during the twenty four hours after each injection the dose should be reduced In the case of patients having almost continual symptoms from nonseasonal allergens it is necessary to progress the dosage cautiously *but gradual progress* may be made unless the symptoms are aggravated after the injections If this occurs the dose is reduced at least two steps on the schedule and then increased more gradually

It has already been pointed out that it is not safe to increase the dose if more than two weeks have elapsed since the previous dose or to repeat the same dose if more than four weeks have elapsed At the end of two months half of the previous dose may generally be given but beyond this limit no accurate estimate is possible

Any change in the extract used for treatment requires caution When changing from year-old extract to a freshly prepared one made and standardized by *the same methods it is best to reduce* the dose to one third to one half of

the previous level In changing from one extract to another standardized by a different system the dose should not exceed one half of the calculated equivalent and if there is also a difference in the age of the extracts one quarter or less should be given In making such changes it is well to give one half or two thirds of the dose believed to be safe observe the local reaction for twenty minutes and give the remainder only if the reaction is not excessive

Actual mistakes in dosage such as using the wrong dilution of antigen are of course inexcusable in allergic treatment The physician giving injection treatment should arrange his time so that he will not work under undue pressure The vials of extract should be kept arranged in an orderly manner so that he knows exactly where each dilution is The label must be read carefully as the antigen is withdrawn To the experienced eye the difference in depth of color of the various dilutions of most extracts is also an added check

Unavoidable errors resulting from mixing of two different antigens in the syringe are discussed in the next section

The possibility of inadvertent intravenous injection may be easily avoided by withdrawing the plunger after inserting the needle before injecting the antigen The risk of this accident is slight when injections are given on the posterolateral aspects of the arm

The effect of heavy exertion immediately after the injection is to hasten absorption of antigen which may in effect produce overdosage The child should be kept in the office for twenty or thirty minutes and he or the parent warned against strenuous exercise for the following hour or two

The routine use of epinephrine or an antihistamine with the antigen injection has been suggested by some writers as a means of preventing reactions This is not recommended as a routine procedure during the period of increasing dosage The avoidance of reactions by careful regulation of dosage is preferable The agents suggested are capable of suppressing local and mild general reactions and may lead to a false sense of security and further increases of dosage until dangerous levels are reached At a certain point the suppressing effect of the drug is no longer adequate and a severe reaction may occur often delayed until after the patient has left the physician s office In the case of patients who are being maintained on a constant dosage the procedure is not open to this objection and may be useful particularly during the pollen season However the use of a somewhat lower dosage without the drug generally produces the same result and seems more logical

MIXTURE OF ANTIGENS

When a child is being treated with several different antigens it is common practice to combine them in one or two mixtures to lessen the number of injections This may be done either by drawing up doses of several antigens into into the same syringe at the time of injection or by preparing a mixture of the desired antigens in a vial for use over a period of time Both methods are open to the objection that if a reaction follows the injection it is not apparent which antigen has caused it

The method of mixing antigens in the syringe allows varying the proportions of the ingredients when desired but inevitably introduces some error in dosage When a solution is drawn into the syringe the glass tip and the needle contain approximately 0 05 ml in addition to the measured volume in the barrel If a single solution is used the same volume remains in the tip after the injection and no error is caused However if a second solution is drawn into the syringe containing the first the material remaining in the tip after the injection is a mixture of the two and the patient received too much of the first solution and not enough of the second The percentage error depends on the volumes measured If 0 05 or 0 1 ml of one antigen is drawn up and followed by 0 6 or 0 8 of a second one the error in the dosage of the first solution may be 50 to 100 per cent On the other hand if the larger volume is drawn up first the percentage errors in both doses are much smaller If both volumes to be measured are very small the error may be lessened by drawing 0 3 or 0 5 ml of diluting fluid into the syringe before adding the antigens Although the error is kept low by always drawing up the larger volume first and using diluting fluid when both volumes are small it cannot be completely eliminated and therefore this method is not suitable for patients who are particularly susceptible to reactions

When using this method great care must also be taken to avoid contamination of stock vials of antigen with other antigens already in the syringe when the needle is inserted This may easily occur if the plunger of the syringe is loose and a partial vacuum has been produced in the vial by repeated withdrawals of fluid without allowing air to enter

The preparation of a mixture of antigens in a vial for the individual patient avoids the difficulties and errors involved in mixing the antigens in the syringe It has the disadvantage that the proportions of the various antigens are determined when the mixture is made and that any change in dosage of one requires a proportionate change in the doses of all other components If the patient is unable to tolerate increasing doses of one antigen the doses of others which might be well tolerated must also be held down while the mixture is used When such a mixture produces local reactions which delay the normal increase of dosage it is best to abandon the mixture and give the various ingredients separately until it is apparent which one is causing the difficulty

In preparing antigen mixtures the proportions of the ingredients must be carefully considered so that the progression of each will approximate the schedule of doses appropriate to the class of sensitivity to that antigen For example if a child having both early and late hay fever reacts to ragweed in Class B and to grass pollen in Class C a mixture of 3 or 4 parts of grass pollen to one of ragweed might be used

If many different antigens are included in one mixture the total dosage of the mixture should be kept moderately below the sum of the doses of each ingredient that might be given separately However the total dosage may be considerably higher than would be a safe dose of any one of the components separately With complex mixtures it is safest to proceed carefully in the early

stages of treatment since too rapid an increase of any one antigen in the mixture may cause difficulties which delay treatment with all the other antigens

On the other hand the eventual top dose of the mixture should be calculated to furnish a reasonable maintenance dose of each antigen according to the classification of the patient s reaction to it If the highest dose of the mixture falls far short of this goal it is better to use the antigens separately Unless the final dose of each ingredient is so calculated the use of complex mixtures often results in grossly inadequate treatment with all the components

DESENSITIZATION WITH FOOD ANTIGENS

Although the avoidance of such important foods as milk eggs and wheat is difficult and tedious it is usually a more satisfactory procedure than attempting to desensitize the patient with those antigens In the case of infants and children under 5 years of age one may be encouraged by the statistical chance of spontaneous recovery in a few years Therefore injection treatment with food antigens is not recommended under ordinary circumstances Kesten Waters and Hopkins have outlined schedules for *oral desensitization* with the principal foods which may be tried but are not successful in every case The general principle is to administer gradually progressive doses by mouth daily until the patient is able to tolerate a normal serving

INJECTION TREATMENT WITH BACTERIAL ANTIGENS

In allergic diseases where infection is a factor the use of bacterial antigens such as vaccines and filtrates for injection treatment is a common practice Less is known of the rationale and immunologic effects of these injections than in the case of inhalant antigens Studies of their efficacy are less susceptible to rigidly controlled observations but clinical use over a period of many years indicates that they are of value Their use may fall into two categories (1) in those cases where there is definite clinical evidence of bacterial sensitization and (2) in the cases of inhalant allergies where the existence of bacterial sensitization is questionable but frequent respiratory infections act as secondary precipitating causes of attacks Since the use of mixed bacterial vaccines for the prevention of colds in nonallergic persons has been generally discredited the latter type of use might reasonably be questioned However the experience of many who have used vaccines extensively in treatment of allergic children indicates that they are probably more effective in the allergic than in the nonallergic child possibly because the existence of lesser degree of bacterial sensitizations is not always demonstrable in advance Since injections of vaccines or filtrates in this type of case are usually combined with injections of house dust or other inhalant allergens the addition of the bacterial antigen does not involve any material expenditure of time or effort On the other hand the use of such mixtures makes it difficult to say how much of the benefit noted has been gained by the use of the bacterial antigen

The type of bacterial antigen most often used is vaccine composed of the bodies of bacteria separated from the culture medium killed by heat and re

suspended in saline Some authors have preferred antigens prepared by the mechanical disintegration of bacteria since heat is known to alter the antigenicity of certain proteins others recommend heat killed vaccines to which specific antibodies have been added and still others prefer filtrates of broth cultures in which the bacteria have been grown until they begin to undergo autolysis liberating into the culture medium antigens which are originally components of the body of the organism No obvious advantages of any of these other preparations over the heat killed vaccine have been established

The vaccine may be an *autogenous vaccine* prepared from cultures of the upper respiratory passages or sputum of the individual patient or a *stock vaccine* containing a mixture of the prevalent strains of the common respiratory organisms An adequate stock vaccine must contain several strains each of *Pneumococcus Streptococcus viridans* and *hemolyticus Staphylococcus aureus* and *albus Neisseria catarrhalis Hemophilus influenzae* and *Klebsiella pneumoniae* in order to include the most common organisms to which the child may be exposed

The preparation of an autogenous vaccine for the individual patient obviously requires the availability of an adequate laboratory and involves additional expense It is open to the objection that the bacterial flora of the respiratory passages may be greatly changed when antibiotic therapy is used so that the organisms contained in the vaccine may have been eliminated before an adequate dose has been reached in the injection treatment For these reasons the use of autogenous vaccine is best limited to those cases in which there is definite evidence of bacterial sensitization and where repeated cultures show the same organisms persisting over a period of time despite the use of antibiotics When an autogenous vaccine is used it is usually combined with stock vaccine in hopes of increasing resistance to both present and possible future infections

Patients with marked bacterial allergy may have severe constitutional reactions to excessive doses of bacterial antigens These reactions usually consist of an exacerbation of the symptoms of the patient s disease and differ from the general reactions to injections of inhalants in several respects They are less often associated with a marked local reaction the onset of the reaction is usually delayed several hours or even a day and the symptoms may persist for several days The distinction between a reaction to an injection of vaccine and the natural fluctuations in the severity of the disease is therefore less apparent than in the case of inhalant antigens One must often exercise considerable judgment in deciding after the first few injections whether or not the patient is being temporarily made worse by each injection

The strength of vaccine suspensions is expressed either on a volume basis or in terms of the number of organisms The 1 per cent by volume suspension contains 2 to 5 billions of common respiratory organisms per milliliter the number varying for different species This is usually the maximum strength needed and may be used as the concentrated vaccine from which dilutions are prepared The safe initial dose of such a vaccine varies greatly with the degree of allergy to the organisms included which cannot be measured by skin tests It is therefore safest to give as the initial dose not more than 0 1 ml of a 1 1 000 dilu

tion and to note the effects carefully The local reaction is of less importance than in the case of injections of inhalants but painful swellings lasting for two or more days call for caution If there is any untoward reaction to the trial dose one should drop back to 0.1 ml of a 1 10 000 dilution When a satisfactory initial dose has been found one may proceed with injections once or twice a week at first doubling the dose each time then proceeding more slowly as indicated in the accompanying table (Table XVI) until a dose of 0.1 to 0.2 ml of the concentrated (1 per cent) vaccine is reached This dose may then be repeated every 2 to 4 weeks for maintenance

TABLE XVI

DOSAGE FOR VACCINE IN BACTERIAL ALLERGY

DOSE			
1	1 1 000	dilution	0.1 ml
	1 1 000	dilution	0.2 ml
3	1 1 000	dilution	0.4 ml
4	1 1 000	dilution	0.8 ml
	1 100	dilution	0.1 ml
6	1 100	dilution	0.3 ml
7	1 100	dilution	0.6 ml
8	1 10	dilution	0.1 ml
9	1 10	dilution	0.15 ml
10	1 10	dilution	0[illegible] ml
11	1 10	dilution	0.3 ml
12	1 10	dilution	0.4 ml
13	1 10	dilution	0.6 ml
14	1 10	dilution	0.8 ml
1	Concentrated†		0.1 ml

Dose given weekl
†Conc nt ted cc ne ontain 1 pe c nt of p ked o g ms by volum

If house dust is being injected into the same patient the dust and vaccine may be combined in a proportion of 9 parts dust to 1 part vaccine after the first trial doses have been given separately

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Chapter 11

ALLERGIC RHINITIS

TERMINOLOGY

As the name implies allergic rhinitis is an allergic inflammation of the immediate urticarial type involving the nasal mucosa It is one of the atopic group of diseases apparently related to the same hereditary predisposition as asthma and infantile eczema and frequently affects the same children who have *these diseases It may be due either to pollens or to allergens with which the* patient has contact throughout the year In the former case it has a typical seasonal incidence corresponding to the period of pollination of the causative plant and is called *hay fever pollinosis* or *seasonal rhinitis* Allergic rhinitis due to other causes is called *nonseasonal* or *perennial allergic rhinitis* A large proportion of the allergic patients are affected both by pollens and by nonseasonal allergens so that symptoms are present throughout the year but become worse during the pollen season

The term *vasomotor rhinitis* is also applied to nonseasonal allergic rhinitis In a strict sense these two terms are not actually interchangeable as vasomotor rhinitis is a designation descriptive of the nature of the pathologic change while the term allergic rhinitis implies a specific immunologic mechanism A great majority of the cases of vasomotor rhinitis in children are due to allergy to extrinsic factors or to infectious agents but others result from nonallergic irritants or from undetermined causes

INCIDENCE

Allergic rhinitis is the commonest of the atopic diseases and it has been estimated that 5 to 8 per cent of the population of the United States are affected by it A large proportion of these cases develop during childhood The onset

of nonseasonal allergic rhinitis may occur during the first year of life Seasonal hay fever is not usually diagnosed before the age of 4 or 5 years but suggestive symptoms may be manifested earlier Both sexes are equally affected Accurate information on the relative susceptibility of different races is lacking but it appears that none are immune Because of the great importance of the pollens of certain plants such as ragweed in the causation of allergic rhinitis the incidence varies considerably in different geographical areas Allergic rhinitis beginning in childhood usually persists into adult life with little or no tendency to spontaneous recovery

ETIOLOGY

As in all atopic diseases susceptibility depends on a predisposition which is apparently genetic although the heredity cannot be traced in every case Actual sensitization results from contact with allergens Because of its function of cleaning and warming the inspired air the nose is heavily exposed to dusts suspended in the air a large portion of which are deposited on the surfaces of the turbinates As a result of this contact inhaled allergens are the most important cause of allergic rhinitis Foods are less frequent causes but are relatively more prominent in the youngest age group Infections of the upper respiratory tract may be related to allergic rhinitis either as causative factors or as complications Certain cases of allergic rhinitis in children of all ages are apparently due to bacterial sensitization associated with infections of the tonsils adenoids and sinuses On the other hand children with allergic rhinitis caused by extrinsic allergens are very susceptible to upper respiratory infections because of the effect of the allergic reaction on the resistance of the mucosae and the interference with aeration and draining The occurrence of nasal polyps and of hyperplastic sinusitis strongly suggests the presence of bacterial allergy In their absence the establishment of the causative relationship of bacterial sensitization to allergic rhinitis is not easy However whether infection is the cause of a particular case of allergic rhinitis or a complication secondary to its presence its recognition and treatment are important in order to attain a satisfactory therapeutic result

PATHOLOGY AND PHYSIOLOGY

The gross changes in the nasal mucosa during allergic rhinitis are readily observed with the nasal speculum During the acute stage the membrane is moderately swollen and red because of the engorgement of the blood vessels There is usually an abundant thin mucoid secretion In chronic cases the edema of the mucosa is often more marked but the hyperemia is less and so the color is a dull grayish red In the most extreme cases it assumes a pearly gray appearance which is very characteristic but this degree of edema need not be present to make the diagnosis Nasal polyps may be present particularly in older children with associated chronic sinusitis The secretion is usually less profuse in chronic cases but still mucoid Histologic study of the membrane shows the goblet cells and mucous glands to be hypertrophied and actively

secreting The mucosa shows infiltration of lymphoid and eosinophil cells and eosinophils are also present in the mucoid secretion

The production of these histologic changes in allergic rhinitis depends upon dilatation of small blood vessels of the nasal tissues transudation of fluid through their walls to produce edema and increased secretory activity of the mucous glands All of these activities are consistent with the actions of histamine which is presumably released as a result of the antigen antibody reaction and are suppressed more or less completely by adequate doses of antihistamine drugs

SYMPTOMS AND DIAGNOSIS

Symptoms—*During the acute stage the nasal mucosa is congested usually* with partial but rarely complete blockage of the nares The rhinorrhea is marked but the watery secretion unlike that of infective rhinitis rarely causes irritation of the nares and upper lip In hay fever the eyes are usually involved with redness of the conjunctivae and lacrimation In severe cases the eyelids may be edematous and chemosis of the conjunctivae may occur Similar involvement of the eyes may accompany acute rhinitis due to other allergens but less frequently than in pollen allergy

Itching of the eyes nose palate and pharynx is a striking symptom in acute cases Often the itching of the nasopharynx is referred to the ears and occasionally the skin of the entire face and neck seems to itch in severe cases

Sneezing is a characteristic feature This characteristically occurs in paroxysms of several sneezes in rapid succession Paroxysms are readily induced by a variety of nonspecific stimuli such as change of temperature draughts dusts and odors of any type and bright sunlight Severe acute allergic rhinitis may cause a degree of lassitude and easy fatigue but not the aching malaise or fever that accompanies many colds

In the chronic stage nasal congestion and blockage of the nares are usually the most troublesome symptoms These symptoms vary in severity from time to time and may affect the two nares alternately but are usually worse in the recumbent position If blockage is persistent it may lead to habitual mouth breathing

Sneezing is less frequent than in the acute stage but still occurs in paroxysms most often in the morning and as a result of the nonspecific stimuli previously mentioned Itching is also less marked in the chronic state but persistent itching and blockage of the nares may lead to a habit of rubbing the nose described by Bowen as the allergic salute The conjunctivae are only occasionally involved in chronic allergic rhinitis

The periodic recurrence of symptoms is very characteristic and depends on the causative allergen Because of the constancy of the seasons of pollination in a given area hay fever may be expected to occur within a few days of the same date each year During the season the symptoms are apt to be worse in the early morning which is the time at which most plants are most active in releasing pollen and decrease considerably during hard rain Rhinitis due

to atmospheric mold spores has no fixed season but occurs throughout the warm months Symptoms due to indoor contacts such as pets or household furnishings are apt to occur in certain houses regardless of season While house dust allergy generally causes symptoms throughout the year these are likely to become more severe in the fall when cold weather requires keeping windows closed and using artificial heat which tends to dry the air and to spread dust by convection currents

Differential Diagnosis —In the diagnosis of allergic rhinitis the chief differentiation is from recurrent or chronic infective rhinitis Although there are many similarities between the two diseases the distinction should not be difficult in the typical case Fever and sore throat common symptoms of the acute cold are not present in uncomplicated allergic rhinitis Sneezing may occur in either disease but paroxysms of several sneezes in rapid succession are usually indicative of allergy Although there may be some itching of the nose at the onset of a cold marked itching of the nose and eyes which persists for several davs suggests allergic disease The onset of both conditions may be accompanied by profuse watery discharge but in infective rhinitis this usually becomes mucoid or purulent in the course of a few days The discharge of allergic rhinitis is much less likely to produce redness or irritation of the nares and upper lip If smears of the discharge are stained the presence of eosinophils is diagnostic of allergy but the absence of eosinophils from one smear does not exclude the possibility

The appearance of the nasal mucosa may or may not be helpful The typical pearly gray appearance is seen only in severe chronic allergic rhinitis In acute cases the appearance is not distinctive

The time and circumstances of symptoms are important Occurrence simultaneously with colds in other nonallergic members of the family naturally suggests infection while onset at the time of an important pollen season or after some unusual environmental exposure suggests allergy Hay fever may not be recognized during the first year of symptoms but when the periodicity of seasonal recurrent becomes apparent it should present no problem

The history of previous atopic disease in the child or his immediate family naturally suggests the suspicion of allergy but is not conclusive evidence

In considering the differentiation between allergic and infective rhinitis it is important to realize that the two conditions often occur together Children with nonseasonal allergic rhinitis are unusually susceptible to ordinary colds and the symptoms of the cold may seem to be merely an exacerbation of the chronic allergic state When infection is superimposed on allergic rhinitis many of the criteria mentioned become confused Fever and sore throat are common manifestations The nasal secretion becomes more or less purulent and smears show a preponderance of neutrophils rather than eosinophils Under these circumstances the presence of the underlying allergic condition may not be readily discernible by clinical or laboratory evidence

While the differential diagnosis of allergic rhinitis should logically precede attempts to determine specific allergic factors in doubtful cases skin tests may be an important aid in the differentiation If the rhinitis is of long standing and there is a personal or strong family history of allergy skin tests with the

important inhalants are amply justified and may demonstrate a background of allergic rhinitis the symptoms of which are obscured by almost constant superimposed respiratory infections

It should be borne in mind that the maxillary ethmoid and sphenoid sinuses are present at birth and the frontals develop during the first four years The maxillary and ethmoid cells may be involved in acute infection by the extension of rhinitis at any age the sphenoids and frontals in older children Less often the sinuses of small children may be involved by chronic infection manifested by nasal and postnasal discharge partial obstruction of the nares and persistent mild pharyngitis Transillumination of the sinuses is not often helpful in small children because of their incomplete development Roentgenograms are of great diagnostic value and should be made in doubtful cases (Figs 4 5 and 6)



Fig 3—X ray of nasopharynx for adenoids Hypertrophy of adenoid tissue in 10 year old girl as revealed by lateral soft tissue x ray of nasopharynx

Other diseases of the nose to be distinguished from allergic rhinitis are foreign bodies polyps congenital malformation and hypertrophied adenoids Careful examination of the nose and throat should reveal these conditions Palpation may be helpful in the diagnosis of adenoids but a lateral x ray examination of the soft tissue of the nasopharynx is usually more satisfactory to demonstrate them clearly (Fig 3)

Etiologic Diagnosis—As in all allergic diagnosis the history of the time place and circumstances of attacks or exacerbations of persistent rhinitis is of great value In cases of pollen allergy a definite statement of the dates of sea

sonal recurrence often clearly indicates the causative agent A prolonged period of symptoms during the warmer months suggests either a succession of different pollen factors or allergy to mold spores Symptoms becoming worse at the onset of cold weather in the fall and persisting into the winter suggest allergy to house dust for the reasons noted in the section on symptoms Rhinitis due to bacterial allergy tends to show exacerbations at the times when upper respiratory infections are most prevalent usually early in the fall and again in midwinter In nonseasonal rhinitis the occurrence of exacerbations in certain houses or other places and under certain circumstances may direct suspicion to specific allergens

In addition to attempting to relate the occurrence of symptoms to contacts with various allergens the history should include a detailed account of all unusual contacts with allergenic substances This gives the information needed for choosing skin tests so as not to overlook potential factors



Fig 4 —Acute sinusitis of left antrum in 13 year old boy with chronic perennial allergic rhinitis X ray reveals presence of superimposed infection

Another important point to be included in the history is the use of vasoconstricting nose drops such as ephedrine and Privine Prolonged and frequent use of these drugs causes a loss of normal tone of the vessels of the mucosa and may produce a vasomotor rhinitis indistinguishable from chronic allergic rhinitis This condition may be superimposed on a true allergic rhinitis or if the use of the nose drops has been started for a transitory condition the changes in the membrane may be almost entirely secondary to their use

In order to evaluate the impressions as to possible etiologic factors based on the history skin tests are needed However since uncomplicated allergic rhinitis is not a dangerous disease or serious disability the parents may be reluctant to subject children below the age of 5 years to this somewhat uncomfortable procedure During the first three years of life there is some reason for the physician to join them in this view since direct skin tests in infants usually



Fig 5—Hyperplastic sinusitis Markedly thickened membrane of left antrum in 6 year old girl Right antrum shows slight diffuse clouding

give small reactions which are often difficult to interpret and the symptoms of seasonal hay fever during the first season are not always accompanied by a positive skin test However there is no definite age limit and the decision in the particular case should depend upon the severity and persistence of symptoms If it is felt necessary the procedure of passive transfer may be used At the age of 3 or 4 years the performance of a small number of direct tests is usually perfectly feasible Often testing with even a half dozen inhalant and pollen antigens carefully selected on the basis of the history will give a reasonable etiologic diagnosis to serve as the basis for the initial treatment This diagnostic study may be amplified later After the age of 5 or 6 years the performance of reasonably thorough testing is usually not difficult if ten or twelve tests are done at each visit

The number and choice of skin tests depends on the history If the rhinitis is strictly seasonal in incidence a relatively few tests with pollens appropriate to the season and area may suffice On the other hand investigation of non seasonal rhinitis requires testing with a group of ten or fifteen basic inhalants to which almost all children have contact supplemented by those of the less common factors to which the history indicates exposure Since the perennial occurrence of rhinitis may obscure symptoms due to pollens the tests should include at least two or three of the most important pollens in the area If these pollens show definite reactions a greater number should be tested



Fig 6—Hyperplastic sinusitis with mucocele in right antrum and extensive changes in left antrum in 5 year old boy with symptoms of perennial nasal congestion

Since foods are only occasionally important factors in the etiology of aller gic rhinitis and the number of different foods eaten by older children is large complete skin testing with foods is not warranted in this disease Ordinarily tests with a dozen or so of the principal foods chosen to include such common allergens as milk egg wheat chocolate chicken beef fish apple orange tomato peas and potato suffice If these initial tests show impressive reactions in any particular group a greater variety of foods in that group may be added

Two plus or three plus reactions to skin tests with inhalant allergens to which the child is exposed are presumptive evidence of significant clinical sensi tization One plus reactions may be considered significant if contact is unusually great as in the case of feather pillows or if the skin reaction is definitely corro borated by the history However it is well to confirm these slight reactions by

testing with stronger extracts of the same antigens if available In allergic rhinitis reactions to skin tests with food allergens are only suggestive of clinical allergy and should be confirmed either by history or elimination diets before being considered important

Skin tests with bacterial allergens are not helpful in deciding the importance of infection in the causation of allergic rhinitis Its significance must be judged from the history and the physical examination with special attention to the presence of infected tonsils and adenoids or in older children of sinusitis the physical findings being confirmed by x rays when necessary While the absence of reactions to extrinsic allergens obviously directs attention to infective factors the coexistence of factors of both types is very common and the suspicion of infective factors should be based on positive evidence rather than exclusion of extrinsic factors

TREATMENT

The treatment of allergic rhinitis consists of (1) symptomatic relief with drugs (2) avoidance of the causative agents (3) injection treatment with antigens not easily avoided (4) treatment of infection causing bacterial allergy and (5) general measures The program of treatment for a particular child will usually combine several of these approaches

Symptomatic Treatment—Suitable drugs offer the quickest relief to patients in the acute stage and are a useful adjunct to other forms of treatment For children with relatively mild seasonal allergy who have symptoms only intermittently on days of heavy pollen exposure and those with allergy caused by pollens whose seasons last only a week or two symptomatic treatment with drugs may provide adequate relief Rhinitis which persists over a period of several weeks is less often satisfactorily controlled by drugs alone

The drugs most commonly used in allergic rhinitis are the antihistamine drugs These are particularly effective in hay fever and other acute forms of the disease in which satisfactory relief is usually experienced by 70 to 80 per cent of patients The effects on chronic allergic rhinitis are less striking but still significant with about 50 per cent of patients relieved Some of the principal drugs in this large group are listed in Chapter 4 with preparations adapted to use in children of various age groups The various drugs of the group vary in potency but those most effective in therapy usually cause a relatively high incidence of undesirable side effects particularly drowsiness therefore no one drug may be said to be best (Table II)

In allergic rhinitis it is usually best to prescribe an antihistamine of moderate potency and relatively mild side effects such as Chlor Trimeton or Ambodryl If this proves ineffectual one may change to a more potent drug such as Pyribenzamine On the other hand if it produces undue side effects one may change to a milder drug

Since the symptoms of allergic rhinitis are usually most marked in the early morning hours a preparation for prolonged action such as Chlor Trimeton 8 mg repeat action tablets or Phenergan is desirable at bedtime On the other

hand the symptoms are not necessarily continuous through the day so that doses during the day can usually be given only as necessary without attempting to maintain a continuous effect

The use of antihistamines in hay fever has little effect in preventing or relieving pollen asthma which may accompany the nasal symptoms If this occurs specific allergic treatment is indicated

The use of antihistamine locally in the eyes or nose is not recommended Relief of severe conjunctival symptoms of hay fever is more readily accomplished by the use of the epinephrine and cocaine eye drops described in Chapter 4 Vasoconstricting nose drops such as Neo Synephrine 1/4 per cent give temporary relief but are of limited value since use prolonged beyond 2 or 3 days usually lessens the irritating effect on the sensitive mucosa and may lead to aggravation of the congestion as the initial beneficial effect wears off

When the symptoms are unusually severe as at the peak of the pollen season and the antihistamine drugs are not effective cortisone derivatives or corticotropin gel may be used as a temporary measure Since all of these drugs may cause *undesirable hormonal side effects their use* in a relatively mild disease such as allergic rhinitis is best limited to small doses over a period of not more than one week Suitable doses are cortisone 25 mg or prednisone 5 mg two to four times a day by mouth or corticotropin gel 20 to 40 units injected intramuscularly daily depending on age Usually relief is obtained in two or three days after which the dosage may be rapidly tapered off

No other drugs have proved to be of significant value Atropine and related compounds lessen the rhinorrhea but do not control the other manifestations Ascorbic acid was widely recommended in the past but is ineffectual

Specific Treatment —In cases of severe hay fever or persistent nonseasonal allergic rhinitis symptomatic treatment with drugs is rarely entirely adequate and measures based on determination of the specific causes are usually needed The occurrence of even mild asthma with the rhinitis is an added reason for specific treatment

When the causative allergens have been determined the simplest and most effective measure is *avoidance of contact* if possible This is particularly true in the cases of feather pillows down quilts and animal pets Pollens and molds are less easily avoided Exposure may be lessened by air conditioning or the use of window filters which help to permit restful sleep but are scarcely a satisfactory protection for an active child Vacation trips to an area relatively free of the offending pollen may also be considered Measures for the control of exposure to house dust are given in the Appendix They suffice for control of symptoms in only a few of the milder cases of rhinitis due to this allergen but are helpful as an adjunct to injection treatment

In most cases of rhinitis due to house dust pollens or mold spores *injection treatment* is needed It may also be advisable in the case of other inhalant allergens if complete avoidance is not practical Treatment with pollens is preferably started three or four months before the onset of the season so that the full therapeutic dose is reached before exposure to pollen in the air The same

dose or a slightly smaller one is repeated during the season at intervals of one or two weeks At the end of the season the treatment may be dropped and the same *preseasonal* treatment repeated the following year However better results are usually obtained in successive seasons and the chance of producing permanent relief is greater if *perennial* treatment is carried out the year round This is done by repeating the dose given at the end of the season every three or four weeks through the winter After the first year the total number of injections per year is no greater with perennial than preseasonal treatment and if the same patient is also being treated with nonseasonal allergens the total number of visits is usually considerably less Patients with hay fever who are first seen during the pollen season may be started on *coseasonal* treatment with small doses of antigens The results of this method are less satisfactory than with preseasonal or perennial treatment and concurrent use of antihistamine drugs is usually necessary Injection treatment with nonseasonal allergens may be started at any time and continued throughout the year Details of these various programs for injection treatment are given in Chapter 10

Treatment of Infection—Infections of the upper respiratory tract are frequently associated with allergic rhinitis either as secondary complications or as factors in its causation through bacterial allergy Whether or not there are evidences of the existence of bacterial allergy treatment of these infections is important as persistent or recurrent infection in the allergic child often leads to the development of bacterial sensitization later in life The measures used for treatment are the same as those employed for the same conditions in nonallergic children but the efforts are intensified

In acute tonsillitis acute sinusitis or persistent purulent rhinitis the sulfonamides and antibiotics are useful Cultures of the causative organism are helpful in the choice of the agent to be used If adequate laboratory facilities are not readily available one may prescribe a broad spectrum antibiotic such as tetracycline but if this does not produce relief within four days the advisability of a culture and antibiotic sensitivity tests on the organism should be reconsidered

The occurrence of recurrent or chronic infection of the tonsils and adenoids calls for careful consideration of surgical removal The presence of allergy does not produce any significant additional risk in this operation Allergy is not in itself an indication for tonsillectomy but the increased susceptibility of children with allergic rhinitis to sinusitis and the possibility of development of bacterial sensitization are added reasons for advising the operation if it is justified by the actual evidences of infection in the tonsils and adenoids In the case of children with hay fever the tonsillectomy should not be performed during the season of symptoms and even in the case of children allergic to other allergens it is wise to avoid operation during the seasons of heaviest pollination Further discussion of tonsillectomy and adenoidectomy is given in the following chapter Recurrent hyperplasia of adenoid tissue in children who have previously had a tonsillectomy and adenoidectomy may be treated with radium or x ray

Sinusitis and recurrent infective rhinitis associated with allergic rhinitis may be treated with injections of bacterial vaccines or filtrates While the results of such treatment are less striking than those of injections of pollens or other inhalant allergens there is considerable evidence that they are more effective in allergic children than the use of cold vaccines in the nonallergic child

Treatment may be carried out with a mixed vaccine or filtrate of the common respiratory organisms but if cultures of the nasopharynx show the persistent presence of the same bacteria through successive acute exacerbations and despite occasional use of antibiotics an autogenous vaccine prepared from the patient s cultures may be added If house dust and other nonseasonal inhalant allergens are also being used in injection treatment these may be combined with vaccine in a single mixture Details of treatment are given in Chapter 10

General Measures—If skin tests are not done because of the age or other reasons general precautions to be taken include the avoidance of the most common causes Dust should be minimized by the measures suggested in the *Appendix* *Feather pillows should be replaced with those stuffed with foam* rubber or Dacron and down quilts with woolen blankets The mattress should be enclosed in a dustproof cover Toys should be selected to permit easy cleaning avoiding woolly or fur covered toy animals Contact with pets should be avoided When the specific allergens have been determined by skin tests similar general precautions are still advisable in highly allergic children since there is a strong tendency to develop new sensitizations to antigens with which they have contact

A child s exercise need not ordinarily be restricted because of allergic rhinitis However during the acute stages chilling and undue exposure should be avoided because of the tendency to secondary infections During the pollen season hay fever may be made worse by swimming in fresh water because of the tendency of pollen to float on its surface Diving and swimming under water increases the risk of secondary infection and should be avoided when the rhinitis is active

PROGNOSIS AND COMPLICATIONS

Allergic rhinitis beginning in childhood almost always persists into adult life if not treated With suitable injection treatment using adequate doses of antigen and carried on continuously the sensitizations tend to become less severe over a period of several years and in some cases may decrease to a point where injections are no longer needed Such children cannot safely be pronounced cured as the symptoms may gradually return in the course of years The patient in any case retains the allergic tendency and is susceptible to the development of new sensitizations and other atopic diseases Predictions as to the necessary duration of injection treatment are too subject to error to be justified The parents may safely be told that undertaking such treatment does not mean it will necessarily be needed through life that many allergic children are able to stop after four to five years and that the chances of attaining lasting relief are greater if treatment is begun early and carried out continuously

A considerable number of children with *untreated allergic rhinitis eventually* develop asthma although several years may pass between the onset of nasal and bronchial symptoms The incidence of this complication in untreated cases has been estimated to be 30 to 50 per cent The association of cough with the rhinitis or recurrent attacks of bronchitis *may be early signs of progression* to asthma and occurrence of these symptoms is an added reason for intensive treatment However premonitory symptoms do not always occur and asthma may develop abruptly in the child with allergic rhinitis after a respiratory infection or an unusually heavy exposure to allergens

RELATION OF ALLERGIC RHINITIS TO UPPER RESPIRATORY INFECTION

The nasal mucosa affected by allergic rhinitis is highly susceptible to secondary infection by the common respiratory viruses and bacteria Because of the pre existing edema of the membranes aeration and drainage of the nose is impaired Ordinary colds tend to run a longer course than in nonallergic children and give rise to a higher incidence of otitis media in young children and sinusitis in the older group The development of infection is often manifested by a change in the character of the nasal secretion from clear mucoid to purulent or by malaise and fever The appearance of the nasal mucosa on examination becomes more intensely red However just as the symptoms of allergic rhinitis may be easily mistaken for those of a cold the secondary infection superimposed upon allergic rhinitis may be confused with an exacerbation of allergy until some such complication as otitis occurs

The combination of allergic rhinitis and infection may show several variations in form Typical perennial rhinitis may be punctuated by periodic increases of nasal congestion with more purulent discharge and slight fever Seasonal rhinitis especially the fall type which lasts until the onset of cold weather may end with an infective rhinitis which superficially resembles hay fever but persists for weeks after the pollen has disappeared from the air Children with relatively mild allergic rhinitis which is apparent in the appearance of the nasal mucosa but manifested symptomatically only by sneezing and mild congestion may have frequent and prolonged head colds

In the study of any child who is unusually subject to head colds the possibility of allergic rhinitis as a predisposing cause should be considered The probability of such a factor is increased if there is a personal or family history of atopic diseases or if the child is subject to frequent paroxysms of sneezing at times when he does not have a cold Examination of the nasal mucosa between colds will usually show the edema characteristic of allergic rhinitis but if it is made during the infection the allergic appearance may be lost in the manifestations of infection If the child is seen between attacks the nasal smear for eosinophils may be helpful but during a cold this is usually of no value At this time the question can usually be solved most quickly by skin tests with five or six of the principal inhalant allergens If these show definite reactions a more thorough study of allergies is warranted In children proved by these

means to have a latent allergic rhinitis treatment by allergic methods is usually the most effective means of lessening the susceptibility to respiratory infection

Acute Sinusitis —Because of the impairment of aeration and drainage by the persistent edema of the nasal mucosa children with allergic rhinitis are unusually susceptible to acute sinusitis as a complication of head colds This is usually manifested by a copious and often unilateral purulent nasal discharge Fever and malaise are common manifestations and may occasionally be accompanied by local pain or tenderness over the affected sinus In older children transillumination of the sinuses may show definite clouding In young children with poorly developed sinuses transillumination is rarely helpful in diagnosis but x ray films are usually of great diagnostic value (Fig 4) Treatment consists of facilitating drainage by the use of vasoconstricting nose drops such as Neo Synephrine ¼ per cent or ephedrine 1 per cent during the acute stage In the more severe cases with fever and pain or tenderness sulfonamides or antibiotics are indicated

Chronic Hyperplastic Sinusitis —Persons with atopic tendency are prone to react to sinus infection by the development of chronic hyperplastic sinusitis This consists of a persistent thickening of the lining membrane which may involve all of the sinuses but is usually most marked in the antra and ethmoid cells Such hyperplasia may be apparent by x ray examination in children 3 or 4 years of age whose sinuses are only partially developed Histologically the sinus membrane like the nasal mucosa of chronic allergic rhinitis is edematous and infiltrated with wandering cells of which many are eosinophils Except during periods of superimposed acute infection there is little or no exudate and the symptoms are negligible The diagnosis is usually made only by x ray examination

The development of hyperplastic sinusitis is important prognostically for two reasons (1) such a membrane is very susceptible to repeated acute infections and (2) hyperplastic sinusitis is usually indicative of the presence of bacterial allergy Children showing this change in the sinuses are likely to have allergic rhinitis due at least in part to bacterial allergy and may develop infective asthma Both of these conditions are more difficult to treat than the corresponding diseases caused purely by extrinsic allergens

The hyperplastic sinusitis of children is not readily susceptible to treatment Since it usually results from bacterial allergy injections of stock or autogenous bacterial vaccines are commonly employed but the effect is more to hinder progression than to correct existing hyperplasia Treatment directed against extrinsic allergens which may give skin reactions in the child with hyperplastic sinusitis cannot be expected to affect the existing chronic condition However treatment of the more important allergies to inhalant antigens is indicated in hopes of lessening the tendency to recurrent nasal infections which cause progression Special precautions are indicated to avoid recurrent respiratory infections and to treat such infections promptly and effectively Sulfonamides and antibiotics should be given early in the course of acute nasal infections and regardless of the absence of fever and in severe cases prophylactic use of

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Chapter 12

BRONCHIAL ASTHMA

Bronchial asthma is a characteristic wheezing type of dyspnea in which obstruction of breathing is caused by widespread narrowing of the smaller bronchi and bronchioles and the presence in their lumina of thick tenacious sputum Typical bronchial asthma is one of the atopic diseases and results from allergy to inhaled antigens foods (or occasionally drugs) and infections of the respiratory system

Bronchial asthma is one of the common allergic diseases it has been estimated that 2 to 5 per cent of the whole population of the United States is affected by asthma and the incidence in children is roughly the same Both sexes are affected but in the younger age group boys predominate The onset may occur at any age and is frequently in infancy Bray has estimated that 22 per cent of all cases of asthma affecting children by the age of 10 years start in the first year and 17 per cent in the second year of life

PATHOLOGY

Although asthma is rarely fatal in children the nature of the pathologic changes has been described by Huber and Koessler and others The walls of the smaller bronchi are thickened and the lumina of many are occluded by thick tenacious mucoid sputum Microscopically the epithelium of some of the smaller bronchi may be thrown into longitudinal folds suggesting constriction by spasm of the circular musculature but this change is seen less often than might be expected from the free use of the word bronchospasm in speaking of asthma The mucous glands are prominent and active The mucoid sputum filling the small bronchi and bronchioles is seen to contain neutrophils and eosinophils The lungs are emphysematous and microscopically the alveoli

are distended and many of the septa disrupted Patchy areas of atelectasis are frequently noted Hypertrophy of the right heart especially observed in infants of 1 to 2 years of age results from the strain thrown on the pulmonary circulation

Sputum expelled during the attack most often in conjunction with vomiting is characteristically thick stringy mucus which tends to form small grayish pearls When spread upon a slide these take the form of Curschmann spirals just visible to the unaided eye In stained smears elongated doubly pyramidal Charcot Leyden crystals are also seen and eosinophils are usually numerous When asthma is complicated by superimposed acute bronchial infection the sputum loses its typical features and becomes purulent

PHYSIOLOGY

Basic Mechanisms —Bronchial asthma results from allergic edema of the walls of the smaller bronchi and bronchioles spasm of the smooth muscle of the bronchial walls and secretion of thick tenacious mucus from the bronchial glands The lumen of the bronchi is greatly constricted by the edema and muscle spasm and the passage of air is further obstructed by the tenacious sputum which may completely occlude many of the smaller bronchi The relative importance of edema and smooth muscle spasm in producing the bronchial *constriction has not been clearly established Evidence of spasm is rarely seen* in the portion of the bronchial tree visualized by bronchoscopy during life and some authorities have considered it a less important factor than edema of the bronchial wall

Direct evidence of the occurrence of spasm of the bronchial muscle has been supplied by the study of Schild and his co-workers of bronchial muscle excised from the lung of a patient with atopic asthma who underwent a lobectomy for bronchiectasis When this bronchial muscle was suspended in perfusion fluid after the manner of the Dale test addition of antigens to which the patient was sensitive caused a prompt contraction This important study which has already been referred to in Chapter 7 demonstrated (1) the occurrence of spasm of bronchial musculature of the asthmatic patient (2) that the atopically sensitized smooth muscle like the anaphylactically sensitized muscle of the guinea pig reacts with antigen in the absence of nerve control (3) that this reaction is not inhibited by atropine which blocks parasympathetic nerve impulses (4) that excised atopic lung and bronchial tissue releases histamine when exposed to the specific antigen and (5) that the contraction of bronchial musculature caused by antigen is only slightly inhibited by antihistamine drugs [4]

Since the parasympathetic nerves of the vagus have been known to exert a motor effect on bronchial musculature it has been frequently suggested in the past that asthma depended on a nervous mechanism Eppinger and Hess in 1909 suggested that asthma was a manifestation of vagotonia in which the *parasympathetic motor influence* predominated over the inhibiting effects of the sympathetic nerves Another theory prevalent in the same period attributed the asthma to a reflex action with afferent impulses arising in various

portions of the body for example from nasal polyps and efferent impulses transmitted through the vagus Numerous attempts have been made to relieve persistent bronchial asthma (chiefly in adults) by various operative procedures in which autonomic nerves supplying the bronchi were resected Some favorable results have been reported by various surgeons but in general the benefits have not warranted widespread use of the method or lent support to the neurogenic theory of bronchial asthma All attempts to explain asthma on a purely nervous basis are weakened by the fact that atropine which blocks the motor impulses to the bronchi is not a satisfactorily effective drug for the relief of asthma and more recently also by the work of Schild

As indicated in Chapter 7 the preponderance of evidence indicates that asthma results from the release of histamine and possibly other physiologically active substances in the antigen antibody reaction This chemical mediator can produce the physiologic change in the bronchioles and smaller bronchi independently of nerve control

Secondary Factors —However the smooth muscles vessels and glands on which the histamine acts are under constant dual control by the parasympathetic nerves *whose effects on these tissues in general parallel those of histamine and* the sympathetic nerves whose effects are in general antagonistic While these autonomic nerves are not essential for the reaction their impulses may greatly augment or inhibit it If the basic chemical stimulus is present the nervous influence may at times be the determining factors in the occurrence or failure to occur of an attack This is presumably the mechanism through which psychic stress may affect asthma

When the bronchial tissues are constantly exposed to small amounts of antigen the occurrence of the clinically apparent asthmatic reaction may also be precipitated by various nonspecific factors such as irritating fumes and smoke changes of temperature etc

Ventilatory Change —The bronchial obstruction produced by these basic changes causes marked interference with the ventilation of the lung impeding the passage of air both inward during inspiration and outward during expiration Since inspiration is normally accomplished by muscular contraction involving particularly the diaphragm and intercostal muscles a slight obstruction to the flow of air is automatically overcome by increased muscular effort and by the use of the accessory muscles of respiration Expiration on the other hand normally is to a great extent a passive relaxation of the chest muscles which permits the elasticity of the lungs to force out air Even a slight obstruction may cause expiration to be prolonged and often incomplete since the chest does not reach its normal expiratory position before the next inspiratory effort begins As the inadequate ventilation of the lungs leads to increased respiratory effort the tendency is for increasing quantities of air to remain in the lungs at the end of expiration and for ventilation to become less and less efficient This overdistention of the lungs produces a state of transitory emphysema which at first clears completely between attacks but with persistent asthma becomes chronic and only partially reversible

These effects are readily demonstrable by spirometric tracings in children old enough to cooperate. This procedure consists of recording the volume of air moving in and out of the chest by a metal drum as in the Benedict Roth basal metabolism apparatus. During quiet breathing the drum shows regular small excursions returning at the end of each expiration to a relatively straight base line which slopes upward as oxygen is consumed and the resulting carbon dioxide absorbed by the soda lime in the machine. The normal child is able to increase the depth of expiration by conscious effort, the extra air so expelled being designated the *reserve air*. During a deep inspiration a considerable volume of air (designated as *complementary air*) is drawn into the chest. This extra inspiratory effort does not appreciably affect the volume of reserve air, the total excursion from the height of inspiration to the end of expiration being the *vital capacity*, equal to the sum of complementary and reserve air. The normal child can rapidly repeat this forced respiratory cycle for ten seconds with relatively little loss in the volume of air handled on each breath. The rate of ventilation during such brief periods of forced breathing is called the *maximum breathing capacity*.

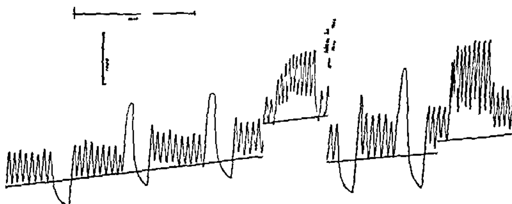


Fig [illegible].—Spirogram of boy 1[illegible] years old with bronchial asthma before and after subcutaneous injection of 0.[illegible] cc of epinephrine 1:1000. Before epinephrine, reserve air 510 cc, expiration prolonged. After deep inspiration, reserve air decreased to 340 cc. Vital capacity 1,380 + 340 = [illegible]. *During rapid breathing expiration is incomplete, not reaching the base line.* After epinephrine had taken effect, reserve air increased to 6?0 cc with more rapid expiration. Reserve air was not decreased after deep inspiration. Vital capacity 1,[illegible] + 640 = 2,380 cc. Rapid breathing was then more efficient. The breaks in the base line indicate where the kymograph was stopped or oxygen added.

Such measurements are not feasible during actual asthmatic attacks but the nature of the ventilatory difficulty in the asthmatic child is readily apparent from tracings made during periods of mild wheezing (Fig 7). In this case the tracing of quiet breathing is essentially normal. The volume of reserve air exhaled after a normal inspiration is *only slightly reduced but the rate* of exhalation is slower than in the normal child. The complementary air is also essentially normal but an attempt to follow a maximal inspiration immediately by a forced expiration as in the ordinary vital capacity measurement brings out the *difficulty in emptying the distended chest*. The volume

of reserve air under these conditions is considerably reduced from that measured after quiet inspiration and the tracing may not return to the previous base line on the same breath. This difficulty is exaggerated when the asthmatic child attempts a succession of rapid deep breaths, the amount of air remaining in the chest increasing with each breath and the ventilation becoming less efficient as effort is increased. Such a tracing explains the effect of exercise or any increase in the depth and rate of respiration in bringing out the symptoms of latent asthma.

The maximum breathing capacity is a satisfactory quantitative measure of the degree of respiratory disability in asthma. The vital capacity, which is more easily and quickly measured with simpler apparatus, is a far less sensitive index of function. The spirometric tracings are of some value in distinguishing asthma from other forms of dyspnea. However, the changes produced by emphysema are identical with those of asthma.

SYMPTOMS

Onset.—The first onset of asthma may be gradual or abrupt. Recurrent attacks of bronchitis following colds may be marked by increasing wheezing and difficulty in breathing with each attack until the diagnosis of asthma is apparent in the course of a year or two. Children with hay fever or nonseasonal allergic rhinitis may progress gradually into asthma with coughing and wheezing becoming more severe in successive attacks. Pollen asthma may also develop gradually in children who have never had hay fever. On the other hand, the first attack of asthma may occur suddenly in the course of an acute respiratory infection after pertussis or pneumonia, or after an unusually heavy exposure to pollen or another allergen. Asthma may also come on within a few minutes after the child has eaten a food to which he is highly sensitive. In such cases urticaria, angioedema, vomiting, colic and diarrhea may occur simultaneously with the asthma.

The Attack.—The typical attack is first manifested by audible wheezing and a repeated hacking cough. The older child tends to sit upright with the shoulders forward so as to utilize the accessory muscles of respiration fully. Infants apparently may be comfortable in the supine position. The respiratory effort is greatly increased but the rate may be only slightly augmented. The chest remains in a relatively distended *position at the end of expiration, the* following inspiration accomplishing little further expansion. Cyanosis occurs only in the most severe cases. The pulse is rapid but the temperature remains essentially normal unless there is coexisting infection. A sudden rise of temperature to from 101 to 103, which subsides within a few hours, suggests that a bronchus has been blocked by a mucus plug. The termination of the attack is often accompanied by vomiting which expels a quantity of thick mucoid sputum.

Percussion of the chest shows the diaphragms to be low in position and limited in excursion. Auscultation shows sibilant or sonorous râles throughout the lung fields, completely replacing the normal breath sounds. The sounds in

one area may be temporarily suppressed if a relatively large bronchus has been occluded by mucus

Periodicity — The symptoms of asthma are characteristically periodic This is not marked in the early stages when the condition usually clears completely between attacks so that the patient feels quite well and physical examination shows no signs of the disease The frequency and duration of attacks varies greatly depending partly on the causative factors In asthma due to inhalant factors the attacks may be very frequent even daily but tend to be of brief duration Attacks brought on by infection tend to be less frequent but usually last several days

After repeated attacks the clearing during the interval is less complete Exertion and exposure to nonspecific irritants tend to precipitate symptoms at any time and auscultation of the chest may show a moderate number of wheezing rales when the patient is not having any distress Thus asthma which at the onset was periodic with attacks clearly related to one or a few specific causes tends to become chronic with the precipitating factors of particular attacks varied and less easily suspected At any stage of the disease prolonged intense exposure to extrinsic allergens or more often persistent infection may cause an attack lasting for a week or more This persistent asthma is often designated as *status asthmaticus* particularly if the response to treatment with epinephrine is unsatisfactory or transitory

DIFFERENTIAL DIAGNOSIS

The coexistence or history of other atopic diseases such as eczema allergic rhinitis or food allergy naturally suggests that wheezing dyspnea is due to to asthma and to a less extent a family history of such diseases contributes to the suspicion The diagnosis is based primarily on the wheezing type of dyspnea its periodicity and the characteristic rales heard on auscultation The relief of the attack by epinephrine is also a helpful sign Examination of the sputum which is an important aid in adults is rarely feasible in children The leukocyte count of the blood may show an increase of eosinophils but this is not sufficiently constant to be a reliable sign

X ray films of the chest show no characteristic change as a result of asthma increased bronchovascular markings may be noted and as chronic cases there is evidence of emphysema However the x ray examination is an essential part of the diagnostic study as it serves to exclude the presence of many other diseases which may cause wheezing and dyspnea by encroachment on the bronchi such as involvement of mediastinal lymph nodes by tuberculosis or Hodgkin s disease opaque foreign body in the bronchus and anomalies of the heart and great vessels

Bronchitis — The differentiation of acute bronchitis and bronchial asthma is not always easy Acute infective bronchitis in infants and children without any personal or family history of allergy may cause wheezing respiration with numerous sibilant and sonorous rales audible on auscultation of the chest This wheezing responds poorly to treatment with epinephrine Fever is usually

present and the leukocyte count may be increased without increase of the eosinophils. Infective rhinitis often precedes or accompanies the bronchitis and nasal smears show a predominance of neutrophils. Such bronchitis, particularly in infants and young children, is not to be considered asthma or in itself evidence of an allergic constitution. A majority of the children so affected who do not have a family history or other evidences of allergy recover completely without subsequent manifestations of the allergic tendency.

On the other hand, repeated attacks of such bronchitis in infants and children may gradually evolve into typical bronchial asthma. This tendency is particularly great in children who have had previous manifestations of atopic disease or have a marked familial background of allergy. In such cases the differentiation between asthma and bronchitis may be theoretical rather than of practical value in treatment and prognosis. The somewhat vague term *asthmatic bronchitis* may reasonably be applied to express this uncertainty. If there is a strong background of atopic disease and successive attacks are increasingly severe, the wisest procedure is to regard the child as an asthmatic patient and study his disease by suitable allergic methods.

Pertussis.—Whooping cough may occasionally cause confusion in diagnosis, particularly when it occurs in children who have had previous attacks of asthma. The history of exposure or of other cases in the neighborhood is helpful. The typical whoop may not be apparent until the end of the second week. Leukocyte counts are valuable, usually showing a well marked increase in the total count and the percentage of lymphocytes. Cultures of the nasopharynx or cough plates may show the specific organisms.

Croup.—In croup or spasmodic laryngitis the respiratory obstruction is laryngeal rather than bronchial. It can usually be distinguished from asthma by the inspiratory stridor, the hollow brassy cough, and hoarseness or aphonia. In most cases of croup there is marked retraction of the soft tissues at the base of the neck during inspiration, while in asthma these tend to be full at all phases of respiration.

Foreign Bodies.—The symptoms resulting from aspiration of foreign bodies into the bronchi may easily be confused with asthma, particularly in infants and small children who cannot give a clear history. The onset of cough and wheezing dyspnea is usually abrupt, and the child's activities at the time may give a clue as to the possibility. The cough is usually persistent and sever[illegible] If the symptoms occur during or immediately after eating, one should ke[illegible] in mind the possibility of a violent general allergic reaction with edema of [illegible] mouth and throat induced by a food to which the child is highly sensitiv[illegible] considering such a possibility, the history of previous eating of the sa[illegible] is important. These reactions may be accompanied by urticaria or it[illegible] the skin and are usually relieved by epinephrine. An attempt at [illegible] bronchoscopy in such a case may be dangerous.

Cough and wheezing due to a foreign body is usually [illegible] relieved by epinephrine. Râles may be limited to one portion [illegible] wheezes heard throughout. X-ray is helpful in the case of [illegible]

bodies If the history is suggestive of a foreign body and the dyspnea is not relieved by epinephrine bronchoscopy should be undertaken without undue delay

Tumors —Adenoma or carcinoma arising inside the bronchus is rare in childhood *Compression of the bronchial lumen by masses outside its wall is* a more common condition These include enlargements of the hilar lymph nodes by neoplasms Hodgkin s disease and tuberculosis and also anomalies of the heart and great vessels In general these extrabronchial lesions are detectable by x ray examination when large enough to cause bronchial obstruction A routine chest x ray of every child being studied for asthma is the best insurance against confusing them with asthma

Pancreatic Fibrosis —Cystic fibrosis of the pancreas also called mucoviscidosis is commonly associated with persistent infections of the upper and lower respiratory system which may be confused with asthma The respiratory infection may be manifested in early infancy by severe spasmodic cough The obstruction of bronchi by thick tenacious mucus causes a wheezing type of expiratory dyspnea similar to asthma In infancy areas of atelectasis are common

This condition may be suspected from the onset of persistent respiratory infection during infancy which may or may not be associated with gastrointestinal disturbances or abdominal distention The diagnosis is established by demonstrating the presence of excess fat and starch in the stools absence or decrease of pancreatic enzymes and the high concentration of chlorides and sodium in the sweat

ETIOLOGIC DIAGNOSIS

Causative Factors — The specific causative factors to be considered in asthma are inhalants foods and infections Drugs are not a significant factor in the asthma of children Various authorities differ greatly on the relative importance to be ascribed to the three main groups of etiologic agents There is no doubt that their relative importance varies greatly in different age groups The im*portance of foods is chiefly during infancy at which time they play a significant* part in a considerable number of cases After the age of 3 or 4 years their importance decreases rapidly and they are rarely a major cause in asthma beginning after the age of 5 Inhalants particularly house dust are a factor in infancy but become increasingly important in later childhood and adolescence Pollens are not important in infancy but become very important after the age of 5 years Between the ages of 5 and 15 years more than 75 per cent of newly developed asthma is due to inhalants and pollens Infection may be a factor at any age but its importance is relatively greatest in infancy and decreases after the age of 5 years Infection may play a part either as a primary cause in children with bacterial sensitization or a secondary factor precipitating attacks in children sensitive to inhalants

It is important to remember that all three types of factors may affect the same child with asthma so that the possible role of each must be evaluated carefully regardless of the presence of factors in the other categories

History—The usual principles of allergic diagnosis outlined in Chapter 9 are applicable A careful history of the time and circumstances of attacks their seasonal incidence and their relationship to certain activities houses or foods often yields valuable clues as to etiology The occurrence of attacks in certain houses or other specific locations obviously suggests inhalant factors Asthma which is worse in the warm months is apt to be due to pollens or molds that worse in the fall and winter to infective factors house dust or such warm bedding as a down quilt It is important to realize that the symptoms of pollen asthma do not reflect the exposure to pollen as exactly as hay fever Asthma due to ragweed pollen often starts rather late in the pollen season may be worse on rainy days when there is no pollen in the air and often lasts several weeks after the end of pollination This persistence of symptoms is in some cases due to the association of dust sensitization or to infections occurring with the onset of cooler weather The development of asthmatic attacks during or immediately after colds suggests that infection is either a primary or secondary factor The association of urticaria gastrointestinal upsets or exacerbations of eczema with the asthmatic attacks is suggestive of foods as a cause Although a careful history gives valuable clues to the causes of asthma in a particular child confirmation of allergy to extrinsic agents by skin tests and of infective factors by a careful physical examination and suitable cultures is essential As in most allergic diseases the history should also include details of exposure to potential allergens such as feather pillows pets farm animals etc and any peculiarities of dietary habits to insure the inclusion of all possible factors in the group of skin tests to be done

In evaluating the apparent causes of attacks the physician should bear in mind the distinction between the primary etiologic agents which are the true allergens responsible for the sensitization inhalants foods and infections and the nonspecific factors which may precipitate attacks in the sensitized child Among the latter are exposure to cold and damp changes of weather mineral dusts chemical irritants such as smoke fumes and strong odors exertion laughter or even excitement and emotional upsets As previously noted respiratory infections may be important either as a primary cause or as a secondary factor in asthma due to inhalants The secondary factors are important in the general handling of the case but are not to be confused with the actual specific causes Since secondary irritants of this type are not usually antigenic they do not give positive reactions in skin tests

Physical Examination—The physical examination should include careful examination of the nose and throat for the presence of infections of the tonsils adenoids and paranasal sinuses The diagnosis of chronic tonsillitis is based on the history of recurrent or chronic sore throat or previous peritonsillar abscess and on the appearance of the tonsils Persistent hypertrophy is usually indicative of chronic infection but small imbedded tonsils may also be infected Persistent redness of the anterior pillars is a helpful sign but is not always present En

largement of the lymph nodes at the angles of the jaw is also a valuable sign. All of these objective evidences may result from acute as well as chronic infection. Their importance depends upon their persistence or repeated recurrence over a period of weeks or months. For this reason several examinations may be advisable before arriving at a definite decision.

Chronic infection of the adenoids is indicated by recurrent or persistent nasopharyngitis, postnasal drip and hypertrophy which may produce obstructive signs or be demonstrated by x-ray. Obstruction is indicated by mouth breathing, especially at night, nasal voice and impairment of hearing. If the extent of the adenoids is not readily apparent on direct examination, they may be demonstrated by a lateral x-ray of the nasopharynx taken with a technique suitable for soft tissues (Fig. 8).

The presence of a persistent purulent nasal discharge in children of 4 years or older suggests sinus infection, but for establishing the etiology of asthma it is important to recognize both the purulent and the nonpurulent hyperplastic types. Local pain, tenderness or swelling is present in only the most acute cases. In older children, transillumination may be helpful in revealing the presence of exudate in the maxillary and frontal sinuses, but is not a reliable method for the diagnosis of hyperplastic sinusitis and does not reveal changes in the ethmoid or sphenoid cells.

In general, satisfactory diagnosis of sinusitis in children depends on roentgenograms. Demonstration of the presence of exudate indicates a purulent type of sinusitis which may be a cause of bacterial sensitization or a nonspecific factor precipitating asthma in a child predisposed by allergy to extrinsic allergens. Slight clouding may be indicative only of previous infection no longer important. Definite hyperplastic sinusitis is indicated by marked thickening of the membrane and occasionally by formation of polyps within the antral cavities. This type of sinusitis almost always signifies the existence of bacterial sensitization which may be presumed to be a causative factor in asthma associated with it. The presence of hyperplastic sinusitis in a child with asthma is considered an unfavorable sign, since the infective type of asthma is usually more difficult to treat than that due to extrinsic allergens (Fig. 9).

The presence of mucous polyps in the nose is not infrequent in atopic children of the older group. These are usually apparent on examination with a nasal speculum. This condition, like hyperplastic sinusitis, is very suggestive of the existence of bacterial allergy.

Skin Tests.—The suggestions as to etiology contained in the history are followed up with skin tests. The choice and number of skin tests needed for a particular child with asthma depends on the history. In strictly seasonal asthma a few pertinent pollens, the two most important molds, Alternaria and Hormodendrum, and house dust may suffice. Nonseasonal asthma requires the use of the more important inhalants to which the child is exposed, the principal pollens and molds, and a selection of the more important foods, usually a minimum of 24 to 36 tests. Those groups of antigens in which positive reactions are obtained may be supplemented by addition of related antigens not considered important enough to include in the first selection.

For the study of infants and small children the method of passive transfer is preferable to direct testing The reactions obtained are more definite and the desired number of tests can be done without fear of unduly upsetting the child

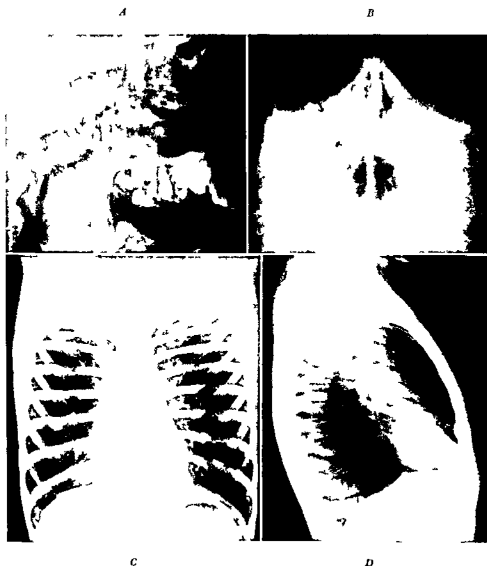


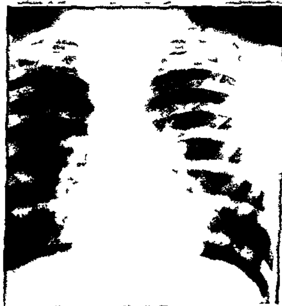
Fig 8—X rays of adenoids sinuses and chest in a 10 year old boy with history of recurrent respiratory infection from years of age and frank asthma since 5 years of age

The interpretation of the results of skin tests follows the principles outlined in Chapter 9 The history physical examination and skin tests are considered together in an attempt to adequately explain the pattern of symptoms More

significance may be attached to a slight or moderate skin reaction which confirms the history than to a marked reaction which cannot be correlated with it Children frequently show positive reactions to a pollen abundant in their lo

A





B

Fig 9—X rays of chest and sinuses in a boy 6 years of age with maxillary sinusitis and infective asthma

cation but have no symptoms during that season Such reactions are probably indicative of potential or future difficulties but are not causes of the symptoms for which treatment is sought Reactions to skin tests with nonseasonal inhalants

to which the child is constantly exposed are less easily checked with the history. If such reactions are moderate or marked (two plus or stronger) they are best considered significant. Reactions to foods are less reliable and, if the past history does not corroborate them, should be investigated by trial diets before they are considered significant.

In difficult cases evaluation of the results may be facilitated by admitting the patient to a hospital where the effects of removal from environmental antigens, changes of diet, and treatment of infection may be carefully observed under controlled conditions.

SYMPTOMATIC TREATMENT

During an attack of asthma the most immediate need is for symptomatic relief by suitable drugs. Since the methods of specific diagnosis and treatment often require considerable periods of time to produce results, symptomatic treatment must be continued in most cases until the effects of the more fundamental measures are apparent. An effective program of symptomatic treatment helps to establish the confidence of the child and family; failure to provide it may lead to discouragement and premature discontinuation of a logical plan of allergic treatment.

Useful Drugs

The actions, doses, and preparation of the three basic groups of antiallergic drugs have been described in Chapter 4. Of these, the epinephrine group and the cortical steroids are of great value in asthma, while the antihistamines are relatively inactive and useful only in combination with other drugs.

Epinephrine Group.—Sympathicomimetic drugs of the epinephrine group are usually the first thought of in the relief of asthma. Epinephrine (Adrenalin) 1:1,000 by subcutaneous or intramuscular injection is effective in a large proportion of patients and is the most rapid in its action. During prolonged attacks the relative brevity of relief may require frequent repetition or the use of more slowly adsorbed forms such as epinephrine in oil or Sus-Phrine. Inhalation of the vapor of epinephrine 1:100 from a suitable nebulizer is also effective, but less so than the injection. Epinephrine has the disadvantage of not being active by ingestion.

Ephedrine is effective by the oral route and is a mainstay in preparations for use at home. Its action is slower and less potent than that of injected epinephrine, but suffices for most mild attacks and lasts about four hours. Because of the unpleasant side effects of nervousness and insomnia, it is often combined with a mild sedative.

One of the most useful mixtures for oral use in asthma of moderate severity is a combination of ephedrine, aminophylline, and phenobarbital.

Ephedrine, Aminophyllin, and Phenobarbital Capsule

Ephedrine hydrochloride	2 mg
Aminophylline	1[illegible]0 mg
Phenobarbital	15 mg

Sig. 1 capsule every 4 hours if necessary.

This formula for the relief of asthma in children of 6 or more years can be varied to suit the needs of the individual case Capsules with smaller doses to be emptied into sweet fluids may be used for younger children If the side effects of ephedrine are troublesome the dosage may be reduced to 15 or 20 mg A stronger effect may be obtained by substituting hyoscine hydrobromide 0 3 mg for phenobarbital If cough is a prominent symptom codeine 8 to 15 mg may be substituted for it Tedral a widely used proprietary tablet contains theo*phylline in place of aminophylline and 8 mg* of phenobarbital It is marketed in scored tablets to permit fractional dosage and in enteric coated tablets for de layed action at night

Isopropylarterenol (Isuprel or Norisodrine) is equally effective with epin ephrine by inhalation and as Isuprel is also available in sublingual tablets com parable in efficacy to ephedrine by the oral route

Cortisone Group—Drugs of the cortisone group are less rapid in their effects on asthma than epinephrine but are usually effective in severe cases which are not controlled by epinephrine When given in the customary manner they pro duce a smoother control of status asthmaticus than epinephrine or aminophylline preventing the occurrence of attacks rather than relieving them after they begin and permitting more continuous comfort and sleep While their side effects over a period of time are more serious than those of the other drugs the immediate effects are not unpleasant as compared to the nervous effects of epinephrine and the nausea often produced by aminophylline

Because of the possibility of the numerous side effects described in Chapter 4 they are ordinarily used only in asthma resistant to other drugs and in status asthmaticus When possible continuous use is limited to periods of a week or two

Cortisone hydrocortisone prednisone and prednisolone are equally effective in suitable doses The latter two are preferred because of less effect on salt and water metabolism Corticotropin by *injection is useful for initiating treat* ment because of somewhat more rapid action

The Antihistamine Drugs—When used alone the antihistamine drugs have only feeble effects on asthma and are not recommended except in combinations *Hydryllin* a proprietary tablet of diphenhydramine (Benadryl) 25 mg and am inophylline 100 mg is a combination which is effective in mild attacks and is chiefly of value for children who suffer excessively from the side effects of ephedrine

The antihistamine drugs are also useful ingredients in cough mixtures for the asthmatic patient The following are suitable proprietary preparations

Benylin Expectorant—Each 5 cc contains Benadryl hydrochloride 13 mg ammonium chloride 120 mg sodium citrate 50 mg chloroform 20 mg and menthol 1 mg in a flavored base Dose ½ to 1 teaspoonful

Histadyl E C Syrup—Each 5 cc contains codeine phosphate 10 mg Thenyl pyramine fumarate 13 5 mg ephedrine hydrochloride 5 mg ammonium chloride 110 mg and chloroform 0 01 cc in a flavored base Dose 1 to 2 teaspoonfuls every four hours

Phenergan Expectorant With Codeine—Each 5 cc contains Phenergan hydrochloride 5 mg codeine phosphate 10 96 mg fluid extract ipecac 0 01 cc potassium guaiacolsulfonate 44 mg chloroform 0 013 cc citric acid 66 mg and sodium citrate 197 mg in a flavored base Dose ½ to 1 teaspoonful

Pyribenzamine Expectorant With Ephedrine—Each 5 cc contains Pyribenzamine citrate 37 5 mg (equivalent to Pyribenzamine hydrochloride 25 mg) ephedrine sulfate 12 5 mg ammonium chloride 100 mg (also available with codeine phosphate 10 mg per 5 cc added) Dose ½ to 1 teaspoonful

Theophylline Derivatives—Theophylline and aminophylline (theophylline ethylenediamine) are similar in pharmacologic actions but since aminophylline is more soluble it is the more widely used drug They are most familiar in medicine as diuretics and vasodilators but exert a potent therapeutic effect in bronchial asthma which cannot be explained on the basis of these recognized actions It appears probable that they relax the spasm of bronchial smooth muscle directly

Both compounds are irritating to the stomach when given by mouth and for this reason it is difficult to secure an effective dosage with either drug given alone by this route However as previously mentioned they are useful in combination with ephedrine or antihistamine drugs in oral medications

The principal uses of aminophylline for asthma are intravenously and by rectum Intravenous injection of aminophylline often gives relief in asthma which does not respond to epinephrine In older children the dose should not exceed 100 mg and the injection must be given very slowly over a period of at least ten minutes Effective doses if given too rapidly are relatively toxic and may cause nausea circulatory disturbances and syncope Great care is necessary in administering the drug intravenously to infants and children of 2 or 3 years as fatalities have resulted from it The dosage should not exceed 50 mg and it is best given diluted in dextrose 5 per cent solution by slow intravenous drip

Intramuscular injection is not advised as the action is slower than when given intravenously and the injections painful Rectal administration is generally preferable to intramuscular

By rectum aminophylline may be used either in solution or as suppositories The effects by this route are slower than those obtained by intravenous injection but also more prolonged Nausea and vomiting occasionally result

Preparations—Aminophylline 100 mg oral tablets One tablet every 4 to 6 hours if needed These are occasionally of value in asthma but the combinations described in the discussion of ephedrine and of the antihistamine drugs are usually more effective

Aminophylline solution 250 mg in 10 cc for intravenous injection Dosage 1 to 3 mg per pound of body weight injected very slowly May be diluted with dextrose solution to facilitate slow injection Repeat after four hours if necessary

Aminophylline rectal suppositories 250 mg The prepared suppositories are suitable for children of 6 years or older One quarter or one half may be given to smaller children Repeat every 8 to 12 hours if necessary

Aminophylline solution for rectal instillation A 0 5 to 2 per cent solution may be used the dosage being *60 to 240 mg according to age repeated every 8* to 12 hours if necessary

Important Adjuncts—*Iodides* are useful adjuncts in the treatment of persistent asthma helping to liquefy and loosen the thick tenacious sputum Saturated solution of potassium iodide 3 to 10 drops in water or milk after each meal and syrup of hydriodic acid 5 ml three times a day are suitable preparations An old and effective treatment for severe persistent asthma in young children is *the induction of vomiting by emetic doses of ipecac The act of vomiting helps to* expel thick viscid sputum which is not dislodged by cough *Codeine* as elixir of terpin hydrate with codeine 5 ml every 4 hours and the related synthetic drugs such as Hycodan 5 mg every 4 hours are of value for cough The use of sedatives except for cough should be sparing Barbiturates in small doses are safe but morphine should not be used and Demerol only rarely with great care

Antibiotics and *sulfonamides* are of great value in treating the respiratory *infections that accompany asthma either as causative factors or as complications*

Other Drugs—The drugs which have been mentioned are believed to be the most effective and adequate for all ordinary cases of asthma The use of many other drugs has been advised and they are effective in some cases These include numerous other members of the epinephrine group which are similar in actions but offer no special advantages Asthma powders containing stramonium to be burned and the fumes inhaled are a time honored remedy of *some value Arsenic has been extensively employed at the Gay Clinic with* good results in some cases but carries a risk of severe toxic reactions and has not been particularly effective in the hands of other physicians Atropine should not be used because of its tendency to dry the tenacious sputum

Home Treatment

The practical programs for symptomatic treatment may be divided into three categories (1) home treatment with drugs administered by the parents (2) treatment by the physician himself in office and home calls and (3) hospital treatment especially of status asthmaticus

The home treatment should be kept as simple as possible recognizing that not all attacks are of equal severity and the alternative use of two different prescriptions is often necessary The mainstay of home treatment is ephedrine For children over 6 years ephedrine aminophylline and phenobarbital capsules and their modifications described on page 173 are *valuable Infants and small* children may be treated with ephedrine 3 per cent aqueous solution the dosage in drops being adjusted to age The use of epinephrine and related compounds by inhalation affords quick relief conveniently in children old enough to cooperate The chief objection to this treatment is that its convenience often leads to excessive and unnecessary use If the nebulizer is used more than three or four times a day longer acting medication should be substituted

For attacks not relieved by these medications aminophylline by rectum in suppositories or solution is the most feasible medication for home use When necessary the parents may be taught to give epinephrine by injection

Cortisone or prednisone is prescribed for use at home when an attack of asthma has persisted for several days despite the above medications Ordinarily its use is continued for only one or two weeks the child being seen by the physician at least once a week In these prolonged attacks the possibility of infection as a causative factor should be considered and antibiotics given if indicated

For persistent asthmatic cough the various antihistamine cough mixtures are useful If the type of cough or auscultation of the chest suggests the presence of thick mucus in the air passages iodides are also prescribed for periods of a week or longer Inhalation of steam is worth trying in acute cases with irritative cough but is not always well tolerated

Treatment Administered by Physician

When the patient is seen during an acute attack the drug of first choice for quick relief is epinephrine 1 1 000 by injection This is given best in small doses repeated every 10 minutes for three or four doses if necessary If this fails to produce an effect aminophylline should be used For children of 6 years or older this is given intravenously allowing at least ten minutes to complete the injection Since the intravenous injection of aminophylline in smaller children is best given by a slow intravenous drip the use of a suppository is generally more practical in treatment at home

If the attack has been brief and is completely relieved by epinephrine no further medication except an oral preparation for future use may be needed On the other hand if the asthma has been increasing over a period of several days it is wise to give an injection of a longer acting preparation such as epinephrine in oil or Sus Phrine in addition In this situation corticotropin gel is also useful A single injection may serve to break up the attack If necessary it may be repeated the next or the second day but if further treatment with drugs of this group is necessary it is preferable to change to an oral preparation such as prednisone or cortisone It should be kept in mind that such continuing attacks particularly in children who are well started on a program of specific therapy are often due to infection and antibiotics may be necessary

Children whose asthma does not abate after intravenous aminophylline are best admitted to a hospital for further treatment If this is not possible a course of steroid therapy must be substituted at home starting with corticotropin gel by injection and carried on with oral use of cortisone or its derivatives

Hospital Treatment

Admission to the hospital for asthma is usually occasioned by failure of the above means to produce relief If they have not had a reasonable trial at home the initial treatment is with epinephrine by injection and aminophylline

by rectum. When it is apparent that these drugs are not adequate or must be repeated several times each day, treatment for status asthmaticus is instituted.

The principal drugs for relief are cortisone and related products. If the condition is urgent, treatment is best started with corticotropin 10 to 15 mg in 500 ml of 5 per cent dextrose administered by intravenous drip. The greatest effect is produced if the speed of flow is slowed to require several hours to complete the infusion. Adequate doses of prednisone or other oral cortisone derivatives are started at once. If necessary, the infusion of corticotropin and dextrose may be repeated daily for two or three days until it is apparent that the condition is improved. Treatment is then continued with oral cortisone derivatives, the dose being reduced gradually after three or four days. In less urgent cases the use of corticotropin is omitted and treatment started with generous doses of the oral cortisone preparations.

Persistence of severe asthma always suggests the possibility of respiratory infection either as a causative factor or a complication. If the presence of infection is suggested by fever or other findings, antibiotic treatment should be started promptly, using tetracycline or another broad-spectrum antibiotic. At the same time, a culture of the nasopharynx is taken and antibiotic sensitivity tests done as a guide to further treatment.

In asthma of this severity, iodides are usually indicated, and sedative cough mixtures should be used sparingly except at night. General sedatives are used sparingly. If it is apparent that the secretions in the respiratory passages are not being eliminated by other measures, the use of ipecac as an emetic may be considered.

At the time of admission to the hospital for asthma, infants and children are often in a dehydrated condition. Dehydration may contribute to the severity of the asthma by drying the bronchial secretions and making them more tenacious. For this reason an adequate intake of fluids, with infusions if necessary, may be of almost primary importance, the type and amount depending on clinical status and electrolyte data obtained from the laboratory.

Oxygen may be helpful in the more severe cases but the patient must be closely watched for evidence of respiratory depression due to carbon dioxide retention. In this age group it is best administered by a tent if available. Use of oxygen by masks or other direct means may tend to dry the bronchial secretions and may be most disturbing to the patient, as placing a tight object over the face may produce more apprehension and physical activity.

When the drugs of the cortisone group are contraindicated for any reason, treatment of status asthmaticus is best started with aminophylline in an infusion given slowly into the vein. As the condition is improved, this may be replaced by aminophylline by rectum and injections of epinephrine. The other drugs recommended for treatment of status asthmaticus are given concurrently.

SPECIFIC TREATMENT

Satisfactory management of asthma over a period of time requires etiologic diagnosis and treatment directed at the cause in essentially all cases. If only a

few mild attacks have occurred the parents may be inclined to temporize in hopes that the condition will be outgrown This occurs in some cases but statistical studies do not justify adopting such a course As a rule the earlier symptomatic therapy is supplemented with treatment directed at the cause the more favorable the results Such treatment may be started in infancy with measures to control exposures to allergens and if necessary injection treatment

Avoidance of Antigens—There is no doubt that the quickest and most effective type of specific therapy is avoidance of the causative allergens When complete avoidance of exposure is possible no other treatment is necessary The effects of avoidance on continuation of the sensitization are not established Between the ages of 3 and 6 years many children lose food allergies which were previously the cause of disease but pollen and inhalant sensitization acquired during this period tend to persist into adult life regardless of avoidance

As has been pointed out previously it is difficult to prove except by avoidance that a particular inhalant allergen reacting in a skin test is actually a cause of symptoms It is wisest to assume that those giving two plus or stronger reactions are important and eliminate contact In patients affected by a multitude of allergens elimination of any one may not immediately produce obvious results but the problem is at least simplified somewhat

The sources of exposure to inhalant allergens common in the household and measures to avoid contact with them have been discussed in Chapter 8 Substitution of other materials usually presents no serious problem However the physician must be prepared for objections from the child or parents when the allergen is a pet dog or cat When a slight reaction to a dog or a cat is noted in a child exposed at home it is well to test this antigen with successively stronger extracts up to 1 000 or 5 000 units per milliliter if necessary in order to elicit a two plus or three plus reaction If such a reaction is produced it should be shown to both child and parent with a flat recommendation that the pet be removed from the house When cooperation in this matter cannot be obtained injection treatment with the allergen should be given but only after a definite warning that it is not the ideal treatment

Complete avoidance of house dust is essentially impossible Measures for minimizing contact are described in the appendix but these can usually be applied only to the bedroom and by themselves rarely suffice to control the asthma of a child highly allergic to this allergen During infancy when the environment is circumscribed and more easily controlled they may serve to postpone the need for injection treatment In older children showing marked allergy to house dust it is usually advisable to start injection treatment as soon as the diagnosis is made Measures for the avoidance of pollens have been discussed in the preceding chapter

Foods which are suspected to be a causative factor on the basis of history skin tests or both are eliminated from the diet until the symptoms are completely controlled over a period of several weeks They may then be added to the diet one at a time at intervals of at least three or four days starting with those against which the suspicion is least convincing If no symptoms follow the addition of a food it is permanently restored to the diet If there is a recurrence after

the addition of a food it is again dropped further trial depending on the degree of reaction Usually it is found that a considerable proportion of the foods showing two plus or three plus reactions in skin tests can be tolerated It should be noted that this type of test can only be carried out during a period when the child is free of symptoms and not receiving symptomatic treatment Attempts to evaluate variations in the severity of asthma while the child is having periodic attacks usually lead only to confusion

Injection Treatment—Injection treatment is usually indicated in asthma due to house dust pollens or molds The use of other inhalant antigens may be advisable in individual cases where it is not feasible to avoid the allergen When necessary such treatment can be begun in the first year of life At this age house dust is the most common inhalant antigen but mold spores may also be a factor

Treatment with nonseasonal allergens may be started at any time with injections once or twice a week until an adequate dose is reached then continued with maintenance dosage every two to four weeks according to the condition of the patient As in hay fever treatment with pollens should be started early enough to permit reaching an adequate dose before the onset of the season Maintenance doses are given once a week during the season then every four weeks during the remainder of the year In those cases where both inhalants and infections are important the inhalant antigens and bacterial vaccines may be used together for injection treatment Details of procedure and dosage for injection treatment have been discussed in Chapter 10

TREATMENT OF INFECTION

The treatment of infection plays an important part in the management of asthma As mentioned repeatedly in previous sections infection may be a specific cause of asthma in children with bacterial sensitization or a nonspecific factor precipitating attacks in children primarily sensitive to inhalant allergens When a child has already been carefully studied and treated by specific measures infection is the commonest immediate cause of attacks lasting several days particularly during the fall and winter months Quite apart from its causative role respiratory infection is a frequent complication secondary to prolonged and severe attacks of asthma

Acute Infections—During the acute stages of respiratory infection the chief treatment is the use of the antibiotics and sulfonamides When respiratory infection is causing asthma the presence of fever is not needed to justify the use of these drugs Cultures of the nasopharynx larynx and antral orifices with tests of sensitivity to antibiotics are the best approach to effective treatment However in order to save time it is wise to start tetracycline or another broad spectrum antibiotic while awaiting the results of the cultures

Care should be taken in using penicillin by injection because of the reactions discussed in Chapter 21 While the severe reactions are not common in children the atopic tendency apparently predisposes to penicillin allergy and intermittent use at variable intervals as is apt to be the case in the treatment of

asthma more often produces severe reactions than continuous courses of injections If penicillin is to be injected for asthma careful inquiry should be made as to any untoward reaction to previous injections If any type of reaction has occurred previously a scratch test with soluble penicillin 20 000 to 50 000 units per milliliter should be done before giving the injection A positive reaction to the scratch test is presumptive evidence of the anaphylactic type of sensitization but a negative result does not exclude the possibility of such a reaction

In children whose asthma has been found to recur promptly with each fresh respiratory infection it is unwise to delay the start of antibiotic treatment until severe asthma has begun In such cases the use of an antibiotic such as tetracycline or oral penicillin early in the course of a cold may avoid considerable trouble In patients with chronic or frequently recurrent respiratory infection prophylactic use of a sulfonamide during the winter months should be considered Sulfadiazine or Gantrisin 0 5 Gm once or twice a day depending on age may be given continuously for several months

Chronic Upper Respiratory Infection —Chronic infections of the tonsils adenoids and paranasal sinuses in children act as a source of recurrent acute infections and in the atopic child may lead to the development of bacterial allergy There are three possible approaches to their treatment (1) prolonged administration of sulfonamides or antibiotics (2) injections of vaccines or related bacterial antigens and (3) surgical removal when feasible In the case of seriously infected tonsils and adenoids surgical treatment is the most practical solution infections of the sinuses are best treated during childhood by the other two methods

Tonsils and Adenoids —The advisability of removing tonsils from children with asthma has for the past thirty years been the subject of discordant opinions which reflect to some extent the changing ideas on the indications for tonsillectomy in general Without attempting to discuss the many views that have been expressed the following opinions of the authors are given in the belief that they are reasonably conservative

The indications for tonsillectomy and adenoidectomy are essentially the same in children with and without asthma namely chronic infection or hypertrophy to a degree producing obstruction When acute exacerbations of infection are the precipitating causes of frequent attacks of asthma the need of operation is more urgent Tonsillectomy has no effect on sensitizations to inhalant or food allergens and asthma in itself is not an indication for operation The degree to which the tonsillectomy may benefit the asthma depends directly on the importance of the tonsillar infection in causing attacks in the particular child

In many instances the onset of asthma has been attributed to tonsillectomy done on a child not previously affected by the disease Such reports while not directly bearing on the treatment of pre-existing asthma naturally tend to cast doubt on the advisability of the procedure Neither of the authors has ever observed this occurrence It is recognized that careful selection of cases for operation proper preoperative and postoperative care good operative technique

and concurrent treatment for allergy to any extrinsic factors may help to prevent its development

Operative removal of the tonsils and adenoids is rarely advised before the age of 3 or 4 years but may be done earlier if the indications are particularly urgent *Removal of the tonsils and adenoids from an allergic child should not be done during the seasons of heavy pollination* especially if the child has pollen allergy The symptoms of asthma should be well controlled before operation and there should be no evidence of acute infection An antibiotic should be given for a day or two before operation It is wise to admit the child to the hospital a day in advance to allow time for adequate examination and preparation Ether anesthesia is well tolerated by asthmatic children but the actual choice of anesthetic should be left to the surgeon and the anesthetist

Sinusitis.—In the treatment of chronic sinusitis of children operative treatment should in general be avoided or postponed as long as possible The removal of enlarged adenoids or nasal polyps may be helpful to aid drainage and aeration

During acute exacerbations antibiotics sulfonamides and vasoconstricting nose drops such as Neo Synephrine ¼ per cent are used as described in a preceding section General care during the chronic stage has been described in the chapter on allergic rhinitis Injections of vaccine may be helpful both to control the sinus infection and to lessen its effect on the asthma

Vaccine Injections.—When surgical treatment is not applicable to respiratory infections which are causing asthma as in infants or in older children with chronic sinusitis injections of vaccines filtrates or other bacterial antigens as outlined in Chapter 10 are commonly used As previously indicated such treatment is less effective than injection treatment with extrinsic allergens but appears justified by the results observed in wide use over a period of years

Either a stock mixed vaccine of the common respiratory bacteria or a special vaccine prepared from the cultures taken from the individual patient may be used Preparation of such a special autogenous vaccine is warranted by failure of stock vaccine to produce the desired results by strong evidence of specific bacterial sensitization and by the persistence of the same pathogenic organism in repeated cultures despite the intervening use of antibiotics When *an autogenous vaccine is used it is ordinarily combined with stock vaccine* in hopes of also protecting against common organisms that may cause future infections

Vaccine treatment is given every one or two weeks during the fall and winter months but may be continued throughout the year with the injections at intervals of a month during the summer

EMOTIONAL FACTORS

Since emotional stress may act as a precipitating cause of attacks in children rendered susceptible to asthma by sensitization to extrinsic allergens or infections the physician must be alert to recognize and detect such factors The initial history may give some preliminary impressions in this regard but these

are apt to be distorted by the biased opinion which the parent has acquired from physicians consulted previously or from articles on medical subjects in lay publications Until the physical factors in the etiology have been carefully investigated and weighed it is premature to attempt a real evaluation of the psychologic factors At the completion of the allergic study and survey of infective factors a thorough discussion of the findings with the parent is helpful both to help the parent in relating the occurrence of symptoms to a logical cause and also to reveal any undue discrepancy between the organic causes which have been found and the periodicity of attacks Such discrepancies suggest further search for less obvious organic factors which may have been missed and also consideration of emotional factors On the other hand if the known physical causes adequately explain the symptoms and the child does not show obvious evidence of maladjustment more is gained by starting treatment for the physical factors than detailed psychiatric study

In those cases where emotional problems appear to be affecting the asthma more careful *investigation of the relationship of the child to his parents siblings* and playmates is warranted The physician accustomed to dealing with pediatric problems should be able to evaluate such adjustments and advise their handling in most cases Specialized psychiatric care is only occasionally needed and must be considered an adjunct to medical treatment of asthma rather than a substitute for it Many of the children in whom asthmatic attacks are obviously precipitated by emotional stress are those who are never entirely free of wheezing because of a multitude of sensitizations and superimposed respiratory infection Previous attempts at allergic treatment may have failed because of the complexity of the problem and the family turns to the psychiatrist since the treatment of other physicians has been ineffective Such children will be helped by psychiatric advice only if at the same time they are given more and better allergic care rather than less It is the duty of the pediatrician to see that this is not neglected

GENERAL MEASURES

In few diseases is adequate discussion with the parents more important than in bronchial asthma They should be aware of the uncertain prognosis of untreated asthma and the benefits of adequate specific treatment instituted early in the course of the disease and continued as long as necessary They should be aware also of the possibility of periodic recurrences despite any program of treatment and should be prepared to administer suitable symptomatic remedies when they occur After adequate study of the *etiologic factors* affecting the individual child these should be carefully explained so that the parents may cooperate intelligently in observing the apparent causes of attacks and regulating the activities of the child so as to avoid them

The physician must be prepared to guide the parents between the *extreme* restrictions which may lead to psychologic invalidism and neglect which may contribute to more severe asthma A reasonable program depends so much

on the degree of severity of the asthma that judgment must be exercised in applying a few general principles to the individual child

Control of Respiratory Infections—A most important consideration is the avoidance of respiratory infections Outdoor play in cold wet weather and activities which may lead to excessive sweating and subsequent chilling are to be avoided Clothing should be suitable for the weather and activities Contact with friends or members of the family who have acute colds should be minimized The first signs that the child himself has a cold call for rest and restriction of activities If previous colds have usually precipitated attacks of asthma a few days out of school for careful treatment at the onset may reduce the amount of time eventually lost

Change of Climate—When asthma persists despite other forms of treatment the question of a change of climate may arise The benefit to be expected from such a change depends on the cause of the asthma The greatest benefit is apparent in cases of severe infective asthma associated with chronic upper respiratory infection particularly hyperplastic sinusitis and it is usually only in this type of case that the change is warranted

Children who have done poorly in cold wet climates are often greatly improved by attending a school in the West or Southwest for a year or two and may return sufficiently improved in general health to tolerate their home climate in later years In addition to private schools there are a few charitable institutions which offer such care for children from families of modest means Aside from the favorable climate such facilities have programs planned for the asthmatic child so that he is less aware of his disability than in a group of normal children Needless to say such a change is not to be advised without due consideration of the problems involved If the child is to be sent away from the family the emotional effect of the separation must be considered If the entire family is planning to make the move the economic adjustment requires great thought In any case the actual change must be made during the period of relative freedom from symptoms

Exposure to Irritants—Exposure to irritating odors fumes and smoke should be avoided as well as heavy concentrations of dust of any sort which may lead to nonspecific irritation or to acquisition of new sensitizations Asthma in childhood may also influence the choice of a future occupation Such children do well to avoid work which involves exposure to known allergens or excessive dust of any type

Exercise—The amount of exercise permissible for the individual asthmatic child must be considered carefully and varied with the phases of the disease Children with seasonal asthma during their free periods and others who have been free of attacks for some time may be allowed unrestricted exercise but even mild wheezing calls for restriction since the symptoms are brought out by running or other sustained exertion They should not be pushed but encouraged to rest when breathing becomes difficult Swimming within reasonable limits during warm weather may be allowed except during seasons of pollens to which they are allergic Swimming in indoor pools during the winter is not

advisable because of the risk of respiratory infection and the irritant effects of chlorinated water

Corrective Exercise —If persistent asthma is causing an emphysematous deformity of the chest corrective exercises designed to improve respiration and posture are advisable These are used daily during intervals between attacks but may also be carried out during periods of mild wheezing In prescribing breathing exercises for the asthmatic child it is important to remember that the deformity of the chest results from persistent failure to exhale completely The ordinary type of breathing exercise used for normal children stresses deep inspiration with expiration essentially passive The emphasis of the asthmatic child should be entirely on expiration After a normal inspiration he should attempt to exhale as completely and for as long a period as possible

Detailed instructions for suitable exercises have been published by the Asthma Research Council of England In general such exercise involves quiet inspiration through the nose and prolonged forced expiration through the mouth Making a hissing sound during expiration serves both to focus the child s attention on the duration of expiration and also to enable the parent or instructor to follow its progress

The chief exercise is in abdominal breathing The child lies on his back with the knees drawn up and a light object of paper or plastic is placed on the epigastrium so that its movement is apparent During expiration the abdomen is drawn in as completely as possible avoiding pauses and jerks During inspiration the abdomen is relaxed and movement of the upper chest avoided No attempt is made to increase the depth of inspiration Older children with emphysema may be taught to aid the expiration by pressing inward and up on the lower ribs with the hands

Having acquired practice in the use of the abdominal muscles for expiration the same respiratory movements are carried out in the standing position while blowing a light object such as a ping pong ball or a ball of crumpled paper across the top of a table covered with cloth[4]

In addition to these breathing exercises arm exercises calling for rotation of the extended arms upward and outward help to correct the postural defect usually associated with emphysema During this procedure respiration is natural with the mouth closed

Other Measures —In older children subject to frequent mild attacks one may well teach the child to give himself a simple oral medication such as ephedrine and allow him to carry a capsule or two with him so that an attack starting at school or play may be quickly controlled without developing into an embarrassing crisis The parent should check daily on the amount of medication taken

Nutrition requires attention if the child has suffered a prolonged series of attacks associated with infection or if the diet has been unduly restricted in attempts to avoid allergenic foods Protein and caloric requirements can be supplied by careful choice of food substitutes but vitamin or mineral supplements may be needed

One of the most important features of the management of asthma in chil
is a confidently optimistic attitude in both the child and the parents This
culcated by the prescription of adequate and readily available drugs for
tomatic relief of attacks together with a careful and logical program for
etermination and control of the causative factors

GNOSIS AND COMPLICATIONS

The widespread impression that treatment of asthma in children is un
sary because of the tendency to spontaneous recovery is not supported by
tics A minority of those who develop asthma in early childhood improve
lolescence *without specific treatment but an equal number become worse*

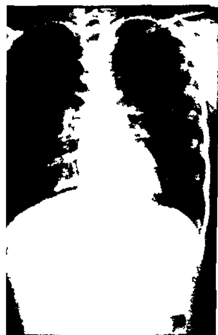


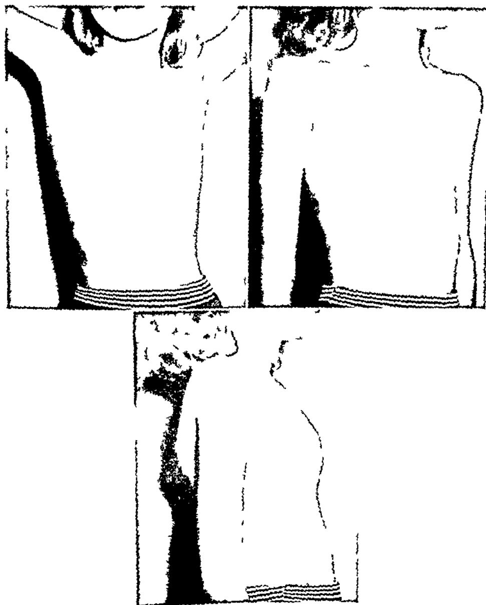
Fig 10



Fig 11

g 10 —X ray of chest of girl 11 years with emphysema following chronic bronchial asthma
g 11 —Lateral x ray of chest in a boy 6 years of age with marked emphysema following
: infective asthma which began in infancy

majority continue to have recurrent attacks Flensborg studied a group
3 children who developed asthma before the age of 5 years and had only
omatic treatment during attacks After periods of 6 to 19 years he found
5 had died 5 of them (1 7 per cent) during attacks of asthma recurrent
s were still suffered by 51 per cent 40 per cent had dyspnea and wheezing
ertion indicating persistent impairment of pulmonary function Only
r cent had recovered and improvement in many of these cases was at
ed to changes in environment



F« 1 —*Deformity* *f chest in* gi l *10* year of age with past history of severe peren ual bronchial asthma following pertuss at 11 month of age A photograph taken at the age of years showed n external che t deformity

The results of specific diagnosis and treatment *are shown by the group of* 449 asthmatic children studied by Rackemann and Edwards In this group there were no deaths due to asthma before the age of 20 years but 4 patients (0 9 per cent) died of the disease between the ages of 20 and 30 At the age of 20 years 71 per cent were free of asthma although 21 per cent had subsequently developed hay fever or other allergic manifestations In 52 per cent the relief resulted from decreased sensitivity in 19 per cent simply from avoiding known allergens Of those continuing to have attacks these were severe in less than half of the cases Specific treatment not only increased the chance of recovery more than threefold but also helped to prevent the persistent decrease of respiratory efficiency due to emphysema and cardiorespiratory complications

Emphysema —The commonest complications of persistent asthma in childhood result from the strain imposed on the ventilatory obstruction on the lungs and heart of the growing child During the acute attack there is always some degree of acute emphysema of the lungs which tends to subside at the end of the attack With frequently repeated attacks the return to normal is less complete and the chest tends to assume a persistently distended form while the lungs lose their normal elasticity and develop the structural changes of emphysema (Figs 10 and 11) The early signs of such persistent deformity is an indication for corrective breathing exercises as discussed previously and for increased effort to control the asthma by all applicable means both specific and symptomatic (Fig 12)

Cor Pulmonale —The autopsy findings in children dying of asthma show enlargement of the right heart in a considerable proportion of cases This is only occasionally noted during life and presumably occurs chiefly or only in the most severely affected children Its development obviously adds to the already severe disability In general the physician is justified in assuring the parents that ordinary asthma properly treated will not affect the child s heart

Subcutaneous Emphysema and Pneumothorax —A relatively rare complication of asthma in children is escape of air from the lungs into the mediastinum and subcutaneous tissues of the neck face and chest This presumably results from rupture of pulmonary vesicles and spread of air along the fascial planes of the tissues When it involves the subcutaneous tissues the diagnosis is obvious because of crepitation on palpation of the swollen areas The extent of spread may be shown by roentgenograms Spontaneous pneumothorax may be associated with subcutaneous emphysema or occur independently during severe asthma of older children

The development of either of these complications may justifiably cause fear of further mechanical impairment of ventilatory and circulatory function However they usually subside promptly with treatment directed at the control of the asthma itself rather than the complication

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Chapter 13

ATOPIC DERMATITIS—INFANTILE ECZEMA

Definition – Atopic dermatitis infantile eczema neurodermatitis and lichen simplex are only some of the names which have been applied to the disorder to be discussed in this chapter It is characterized by an intensely pruritic eruption which usually shows a progressive series of skin changes associated with vesiculation and weeping during the early acute phase and in the later more chronic phase lichenification and alterations in the pigmentation of the skin

Infantile eczema is by far the most common chronic skin disorder seen in early childhood It most often begins at 1 to 6 months of age and onset before the age of 8 to 13 weeks makes the diagnosis suspect Many rashes are seen in the initial neonatal period which are not satisfactorily diagnosed and while the possible allergic nature of a skin eruption is frequently discussed definite classification is impossible

The racial distribution depends largely on the locality in which patients are seen It is not at all a condition limited to blond fair skinned children At least 50 per cent of the patients at clinics in New York City are Negro and it is seen in Orientals and dark skinned Occidentals as well

ETIOLOGY

Although infantile eczema and atopic dermatitis of older children have long been considered allergic diseases and many patients have been treated by allergic methods with apparently good results the etiology in many cases is still not easily established The relationship of specific allergenic factors to the actual production of symptoms is far less direct and obvious than in other atopic diseases Detailed consideration of these problems is essential to a logical program of treatment

Hereditary Factors —The term atopic dermatitis indicates that this type of skin disorder is found characteristically in individuals of the atopic constitutional make up i e they often have a family history of allergy often go on to develop other allergic manifestations such as hay fever asthma perennial rhinitis later in childhood have demonstrable skin sensitizing antibodies and often show a significant eosinophilia in their peripheral blood These features though they do not prove that infantile eczema is a disorder due to hypersensitivity certainly strongly suggest that it falls in this group and that study and investigation directed along these lines may yield significant results In many cases the results are excellent in others disappointing

Specific Extrinsic Allergens —Direct skin tests or testing by the method of passive transfer usually shows the eczematous child to react to a considerable number of extrinsic allergens both foods and inhalants Since both the test and the disease itself are reactions of the skin it might be supposed that the reactions to tests would be closely correlated with the clinical effects of the allergens In actual practice it is found that this correlation is far less than might be expected

For many years food allergy has been considered the prime cause of infantile eczema and atopic dermatitis in older children Undoubtedly this factor may be important but the present opinion of many authorities regarding foods as specific etiologic agents is that they have been grossly overrated This does not mean that food restriction and trial diets do not have a place in the management of infantile eczema but simply that specific proof for this as a causal relationship is often meager Not only must elimination produce relief but the introduction of the food into the diet on several different occasions must produce a flare up in the skin before the food can be considered proved as a specific etiologic agent In the case of artificially fed infants cow s milk is the most frequently suspected food but as other foods are added to the diet they also are subject to suspicion

Inhalants have been implicated by several workers as causes in the pathogenesis of infantile eczema and atopic dermatitis of older children Among the common offending agents are dust animal danders wool molds and pollens There can be no dispute that such a mechanism has been demonstrated The frequency with which it is a factor of importance in cases of atopic dermatitis cannot be stated It is true that when these infants and children are tested positive reactions to inhalants are obtained However when these materials are applied directly to the skin in the form of a patch test it is almost never possible to reproduce the dermatitis In some instances aggravation of the dermatitis may be noted following contact with dogs or cats indicating a causative relationship between exposure and reaction

Sensitization resulting from external contact of the offending agent with the skin is not frequently seen in eczema in childhood Silk and wool are the most important agents in this regard Direct contact with wool is usually irritating to eczematous skin but this is due more often to mechanical irritation than to specific allergic sensitization

Infection —There are some observations which indicate that bacterial infection may be an important etiologic factor in certain cases of atopic eczema

(1) Exacerbation of symptoms occurs during periods of infection in some patients In following a patient this relationship may be repeatedly observed By some workers this effect is regarded as a nonspecific event due to the activation of latent sensitivities by the infectious process However since knowledge is lacking as to the nature of these latent sensitivities this explanation does not materially advance our understanding

(2) A second point which suggests that bacteria or bacterial products (or possibly autogenous antigen modified by bacterial action) are of importance is the occasional child who following the removal of infected tonsils and adenoids makes a dramatic and sustained recovery

(3) A third piece of evidence indicating that bacteria may be important in the pathogenesis of infantile eczema is that the administration of an excessive dose of a vaccine suspension has occasionally been observed to activate the skin process Attempts at reproducing the lesions by application of filtrates or vaccines to the skin by means of patch tests have in our hands been unrewarding however reactions to such tests have been reported in the literature (Storck)

It is difficult to state precisely the relationship between local infection and the development or exacerbation of dermatitis Certainly successful treatment is not obtained unless secondary bacterial infection is eliminated When cultures of the skin are obtained well over two thirds of the cases yield hemolytic staphylococcus and about one third hemolytic streptococcus Not only are these organisms found with greater frequency in this group of children but they are found in much greater numbers than they are in noneczematous skins

The concept of bacterial sensitization is sound what is needed are more objective techniques to demonstrate its etiologic relationship in the individual child

Seasonal Factors—In the older child the dermatitis may be perennial or seasonal In most instances it is worse during the winter than during the summer months This may be associated with the increased amount of time the child spends indoors and is exposed to household inhalants It may be due to the mechanical trauma from the rubbing of heavier and often woolen clothes Often these children are also worse when they have respiratory infections so that there may be multiple factors responsible for this aggravation during the cold season The improvement and change these children show during the warm weather may be stimulated by trips to the beach and salt water baths suggesting a beneficial effect of moderate exposure to sunlight and salt water This series of events is not necessarily effective 100 per cent of the time as we have seen children who have been taken south during the cold weather months in order to improve their dermatitis and who have failed to show any change

Eczema which is worse during the warm weather also occurs The question of pollen sensitivity and the ingestion of certain foods only available during this time is often raised Although they may show positive reactions to intracutaneous skin tests with pollen extracts patch tests with these pollens both the lipid and aqueous extracts do not as a rule give positive reactions Since many of these children have reached the age where they also have nasal allergies the relationship of the eczema to possible pollen factors is difficult to assess Injec

tion treatment with pollen extracts only occasionally improves their skin condition

A hot humid atmosphere often has a deleterious effect on atopic dermatitis because of obstruction of the sweat ducts in the diseased skin Failure of the sweat to escape from the glands causes increased inflammation and itching of the skin

Clinical Studies—Since atopic dermatitis is not readily produced in experimental animals investigations aimed to elucidate its etiology have taken the form of careful clinical investigations seeking not only to relieve the existing dermatitis by elimination of possible etiologic factors but also to reproduce the disease by intentional exposure to the suspected cause In a large proportion of cases it has not been possible to reproduce the lesions characteristic of the disease in a limited and controlled manner It is this failure more than any other which is responsible for the great variety of opinions regarding the possible causes and treatment of this disorder

There are certain other features which complicate the intelligent objective study of infantile eczema Often during the course of the natural history of the disease there are so called spontaneous periods of exacerbation and remission unrelated to any change in therapy or any features which can be elicited from the most careful history Another complicating facet in the study of this disorder is associated with the fact that during treatment it is usually not practicable to work with one variable at a time One often restricts the diet uses various symptomatic measures and gives antibiotics simultaneously so that a clear causal relationship between any of these measures and effects produced cannot be readily ascertained At the conclusion of a therapeutic triumph one may be as ignorant as to the specific causative factor as at the outset Also a therapeutic regimen which has proved to be effective in one case may fail completely when tried in succeeding instances

It is important to point out these difficulties in order to appreciate the complexity of this problem The observation that the child s rash improves when among other things cow s milk is eliminated from his diet is of great satisfaction to the parent and the physician However this per se is not adequate scientific proof that an etiologic relationship exists between the two events In practice one often hesitates to risk the possibility of producing a generalized flare up of the skin by introducing a factor held suspicious but there is no satisfactory laboratory test or other procedure which can be used routinely to establish an etiologic relationship

Patch tests by means of prolonged application of the various foods to the skin have also been tried Except for a few isolated instances the results have been consistently negative Even in those cases where positive reactions were obtained the skin reactions were usually obtained only in a very limited portion of the skin such as the cheek or eyelid and did not indicate the generalized skin involvement so characteristically seen in atopic eczema

The point is occasionally made that in applying the food substance or extract to the skin we are not using the antigen to which the cells are actually sensitive The latter may be a product of the digestive breakdown of the orig

inal food This may be true yet similar negative *results are characteristically* obtained when hydrolyzed food substances are used

Other Factors—The question as to the significance of the immediate type of allergic reaction in atopic dermatitis has not been *settled because of the* difficulty in reproducing the characteristic lesions of the disease To date there is no satisfactory procedure which will do this It has been postulated that in addition to the reaginic or skin sensitizing antibody some other unknown factor is necessary to reproduce the lesions Since we are unable to demonstrate this factor and do not know where and how to look for it this hypothesis must remain a purely academic one

The theory that atopic dermatitis is related to some abnormality of fat metabolism and the therapeutic use of unsaturated fatty acids in the diet based on this concept have failed to stand the test of time

There is no doubt that mechanical irritation by scratching tends to aggravate the acute lesions and contributes to the lichenification characteristic of the chronic stage This vicious circle of itching dermatitis and scratching is a factor to be considered in practical treatment but does not explain the basic mechanism

In older children atopic dermatitis may be related to nervous and emotional factors as implied in the term neurodermatitis This influence is apparently not of significance in the first year of life Since a large proportion of cases of atopic dermatitis in older children are continuations or recurrences of eczema which began in infancy it appears probable that emotional stress acts as a nonspecific aggravating factor rather than a basic cause The nervous mechanisms through which it may influence the skin lesions have been mentioned in Chapter 3 Although not directly pertinent to the etiology of eczema it well to point out that *persistent itching at any age may affect the happiness* and emotional stability of a child and that the disfiguring appearance of chronic atopic dermatitis may be a cause of emotional stress in older children These relationships should be kept in *mind when evaluating the cause and effect* relationship of dermatitis and emotional instability

Etiology in Different Age Groups—A relatively direct relationship of food allergy *to dermatitis appears to be most frequently noted in infancy* while atopic dermatitis in older children is usually found to present a complex and confusing picture of many diversified possible etiologic factors the relative importance *of which may be difficult to elucidate To some extent this may reflect* the tendency of the more complicated cases to persist despite treatment However it also seems probable that cases which are relatively simple at the onset may become more complicated by the development of new sensitizations and that long standing dermatitis is more influenced by nonspecific factors

SYMPTOMS AND PATHOLOGY

Persistent itching is the symptom which is most distressing to the patient Often this is associated with marked discomfort irritability restlessness and insomnia

The eruption in the majority of cases begins on the cheeks between 1 to 6 months of age Rashes which appear before the infant is 2 to 3 months of age

are most likely not infantile eczema This is in agreement with the concept that a certain latent period is necessary for producing the manifestations of hypersensitivity At this age is may be difficult to evaluate the amount of itching associated with the rash This appears as an erythematous finely papular eruption most frequently on the skin of the cheeks where in some cases it may remain The skin involvement may become generalized and in severe cases only small islands of normal appearing skin may be noted against a background of skin with weeping crusted dermatitis (Plate II E frontispiece) Sites of predilection are the antecubital and popliteal areas and about the neck and ears Often the diaper area may be completely spared In other cases there is significant involvement of the inguinal area buttocks and gluteal folds

A fair amount of skin involvement may also be noted in infants on the lateral aspects of the lower leg This may be related to the physical trauma to which these areas are subjected as a result of rubbing The infant lying supine with legs outwardly rotated rubs this portion of the skin against the bed clothes in order to obtain some relief from his itching but usually produces an extension of the skin involvement

A characteristic lesion in the early stage is a vesicle on an erythematous base Often this is not seen as the tops of the lesions usually are scratched off and the entire skin area becomes excoriated There is exudation of serum from the skin which may become secondarily infected and produce yellowish golden brown crusts on the skin There is a fairly regular progression of lesions in the development of this stage usually beginning with erythema papulation vesiculation oozing and crusting Different areas of involvement may show varying stages of development Often there is considerable secondary bacterial infection present as the open excoriated skin sites serve as excellent culture media for bacterial growth It is rather surprising that bacterial infections of serious degree do not complicate this condition more frequently

This may be regarded as the acute stage of the disease and from the viewpoint of symptomatic therapy should be differentiated from the indolent chronic stage A subacute phase of involvement has been described but since this is a separation not associated with any distinctive features it has little practical value

In the chronic form the skin becomes thickened coarse and dry with some alteration in its pigmentation The more common sites of involvement are flexural surfaces of the extremities and the neck although in some cases the entire skin has a thickened lichenified texture In some children the areas of previous involvement may remain lighter in color than the surrounding skin in others there may be increased skin pigmentation (Plate I C D and E and Plate II A frontispiece) Often these areas also fail to tan as deeply as the normal skin following exposure to the sun It may take many months before these areas assume normal skin color In Negro children the same condition may be noted though here the difference may be even more striking with either marked depigmentation or increased darkening of the skin (Plate II B frontispiece)

During this lichenified stage pruritis is not as marked but the cosmetic effect is disturbing both to the older patient and to the parents

Symptoms are essentially the same regardless of age of onset The age of onset may be of some importance in the approach to the study of the possible causative factors in the dermatitis but otherwise do not show any significant differences In the young patient with a long history areas of involvement which are often stubbornly resistant to treatment are areas of friction and trauma such as the wrists and the ankles the back of the heel where there is rubbing from movement of the shoes and the back of the neck where the collar rubs against the skin

Periodicity—*In some eczematous children there is very little seasonal* variation of the lesions and symptoms In others there is a story of improvement during summer months with recurrences in the fall and winter whereas in a still smaller group the lesions flare up more markedly in the summer The *possible relationships of such seasonal variations to seasonal allergens respiratory* infections and climatic conditions have been discussed

Aside from these seasonal fluctuations infantile eczema shows a tendency to spontaneous healing in a large proportion of cases late in the second year of life In those cases that persist through childhood exacerbations and remissions may occur at irregular intervals without necessarily any obvious relationship to specific allergenic factors or to treatment

Pathology—Careful examination of biopsy specimens obtained from these cases of atopic dermatitis have failed to demonstrate any pathognomonic features useful in diagnosis or suggesting further areas of investigation The acute stage is manifested by intercellular edema and small areas of spongiosus of the epidermis hyperkeratosis and acanthosis In the chronic state marked acanthosis is the most striking feature There is perivascular infiltration of the cutis by wandering cells including eosinophils

DIFFERENTIAL DIAGNOSIS

Ordinarily the diagnosis of atopic eczema presents no major problem As was noted the lesions are papular or vesicular on an erythematous base with oozing and the formation of yellow golden crusts Even in the very young infant itching may be quite marked and distressing If the diagnosis is uncertain the subsequent course of the skin eruption and the patient s behavior will clarify the situation within a relatively short time

In the young infant seborrheic dermatitis is the most commonly encountered skin eruption to be differentiated from infantile eczema In the former condition the scalp and intertriginous areas are primarily involved The scales tend to be thick grayish and waxy and the scalp involvement is commonly referred to as cradle cap The axillae and groin are common sites of involvement though the lesions may be more generalized and involve the postauricular area neck and extremities There is characteristically no vesiculation or weeping of the skin and pruritus is absent or slight The lesions are fairly sharply circumscribed occur on an erythematous base and may tend to clear centrally The etiology is not clearly understood but is believed to be related to fat metab

olism In some infants the combination of seborrheic dermatitis and atopic eczema occurs simultaneously so that characteristics of both disorders may be noted

Hill has described a severe form of infantile eczema which he calls atopic erythroderma There is generalized involvement of the skin with extensive scaling and generalized marked redness glandular enlargement and little vesiculation with blueness of the hands and feet and marked eosinophilia There is usually considerable evidence of secondary infection This type runs a protracted course and offers considerable difficulty in management but the principles are the same as in other cases

Leiner s disease must occasionally be differentiated from this group Since the mechanism and etiology of the condition is likewise not understood diagnosis is based on morphology of lesions and course This disorder occurs in young infants during the first to third month There is little itching and no increase in eosinophils in the peripheral blood Diarrhea is common and often severe and protracted Not infrequently their course may be so stormy that intravenous fluids and electrolytes are needed in order to keep these babies alive In two instances where recovery was satisfactory a diagnosis of psoriasis was made before the end of the first year of life

Fungus infection causing eczematous dermatitis occasionally comes up for consideration Only rarely is it possible to isolate any pathogenic agent from the skin The most common site of involvement is the diaper area The lesions are bright red in color with sharp margins Pruritus is slight or absent The fact that some of these cases respond to Vioform or other fungicide therapy is not proof of a fungus etiology

Contact dermatitis is seen in infancy and childhood Certainly poison ivy is numerically the most important cause The distribution of the lesions on the exposed areas of the skin and the history must serve as the guiding factors with regard to the possibility of this etiologic factor The possibility that a contact dermatitis may be superimposed on an atopic dermatitis must be considered It must also be differentiated from dermatitis due to primary chemical or physical irritants not infrequently as a result of too vigorous treatment Patch tests may be helpful A negative patch test does not however rule out the possibility of a contact dermatitis as the sensitivity may not be generalized During the acute phase it is not practicable to test the affected areas of the skin

ETIOLOGIC DIAGNOSIS

In the pediatric literature and in pediatric thinking the idea that foods are the principal incitants of infantile eczema is repeatedly noted yet when this hypothesis is subjected to careful scrutiny and objective study confirmatory data are often lacking There is also evidence that inhalants contacts and infection are occasionally important As was noted earlier since it is often not possible to reproduce the lesion under controlled conditions much of the study is indirect but based on the concept that this is a disorder primarily allergic in origin Attempts at therapy must often be directed along several lines simultaneously in order to obtain success rarely is the elimination of a

single factor followed by a therapeutic miracle As is true for bronchial asthma there are many so called nonspecific factors of much importance in the clinical course of infantile eczema These have been discussed in the section on etiology

History —The manner in which the study and treatment of any case of eczema is to be carried out is based primarily on the history All the pertinent information may not necessarily be obtained during the initial interview but *with careful and thoughtful questioning much material of possible future help* can be obtained

It is obviously not feasible to give a list of all the questions which should be asked the parents Some of the more significant matters to be determined are as follows

1 Age of onset Duration of breast feeding

2 Original site of involvement and sites and rate of subsequent spread

3 Any unusual circumstances surrounding onset of symptoms such as (a) introduction of new foods (b) infection (c) new contacts and (d) untoward reactions if any

4 *Behavior during postnatal period—regurgitation vomiting diarrhea* colic changes in formula and reason for change

5 Contacts at home—feathers wool animals bathing soap

6 Relationship to infection—respiratory gastrointestinal

7 Seasonal variation—summer winter sunlight

8 Detailed account of previous study—local and systemic treatment and response

9 Reaction to drugs—sedatives antihistamines penicillin *sulfonamides* aspirin etc

10 Previous immunization and reaction if any

11 *Manner* of laundering clothes soap detergents or bleaches used

12 Food dislikes and food habits

13 Environmental factors attitude of family degree of reliability and cooperation of family

14 Child s attitude relationship to playmates school mates relationship to siblings anxiety

Physical Examination —Having obtained such data from the history *one is ready to obtain as much help as possible from the physical examination* and laboratory aids The differential diagnosis has been discussed The appearance and distribution of the skin eruption in association with the history will determine the presumptive diagnosis The degree of secondary skin infection must be noted as this may play a significant part in the effective management of the condition There may be obvious pyogenic infection with localized pustules and purulent exudate or the skin may not show any visible evidence of infection yet the regional lymph nodes may be *large firm and prominent* Since most of these cases show a certain degree of skin infection a culture of the skin as well as of the nasopharynx is obtained A white count will often show leukocytosis and varying degrees of eosinophilia It is important to know the bacterial flora that is present and plan antibiotic therapy accordingly Well over two thirds of these young patients harbor hemolytic *Staphylococcus*

aureus in their skin and about one third have beta hemolytic streptococci Many of these patients have identical organisms in the nasopharynx

The possible etiologic effect of infections other than the local secondary infection of the skin lesions has already been mentioned The tonsils and adenoids are the most common site of such infection in children The physical examination should include careful inspection of the nose and throat for evidence of infection the fact being recognized that the diagnosis of chronic infection may require correlation of the history of respiratory infections with repeated examinations over a period of time

If there are other complications such as severe vomiting or diarrhea or occasionally generalized edema the laboratory studies which are needed for satis factory correction of these states should be done In the uncomplicated case there are no clear cut and consistent laboratory changes which shed light on the basic mechanism of this disorder or other metabolic changes

Skin Tests —The astute clinician can do an excellent job in the manage ment of many of the younger patients without resorting to any type of skin test The age of onset is an important factor here The infant who has been on a relatively limited diet can very easily be managed on a food trial basis Cow s milk has long been stressed as an important etiologic factor in develop ment of infantile eczema and its elimination is a logical beginning Since the casein fraction of milk of all the various species whose milk is used for infant feeding is essentially identical the infant who has sensitivity to this fraction will probably show no significant change when he is placed on a formula of goat s milk It seems more logical to eliminate milk completely or to alter its antigenicity by prolonged heating as recommended by Ratner many years ago Substitutes for milk such as soybean preparations meat base formulas or Nutramigen are readily available and usually well tolerated

If the dermatitis does not respond to such simple measures skin tests either direct or indirect are done with the common inhalants and foods Altogether these rarely need include more than 10 or 50 allergens There is little need to include foods which are not given in the child s current diet or which will not be introduced in the near future

The technique to be employed will depend largely on the age of the child and the severity of the skin involvement If the skin is dry thickened and coarse direct skin tests are not satisfactory as the responses to intradermal allergens are often quite sluggish Passive transfer tests are satisfactory and can be done with strong allergens and without fear of systemic reactions All the important foods and inhalants can be tested at one time and a prompt answer obtained If the patient gives a history of vomiting angioedema or hives fol lowing the ingestion of a food such as egg or peanut he should not be tested by the direct route as there is a decided risk of a constitutional reaction Under such circumstances indirect tests by the passive transfer method are indicated

In view of the discrepancies noted in the discussion of etiology of what use are the results obtained on skin testing in helping us outline a rational therapeutic regimen? One often learns little from this procedure but oc-

casionally some highly useful information is obtained The skin tests are only useful if in conjunction with the history and the subsequent clinical course of the patient an etiologic significance can be demonstrated A positive reaction to a food does not necessarily prove that it is of clinical importance In order that this may be established withholding the food must be associated with clinical improvement and adding the food must be followed by exacerbation This is apparently a simple procedure In practice however especially in the older child it may be difficult to maintain adequate nutrition while carrying out this type of procedure in a manner suitable to accomplish the desired result It is also to be remembered that a substance known from the clinical history and observation to be a causative or aggravating factor may occasionally fail to give a positive skin test The significance of reactions obtained to inhalant allergens will be discussed in the section on specific treatment

Skin tests with bacterial allergens in the form of vaccines culture filtrates or extracts are not helpful Positive reactions of the delayed type merely indicate past exposure and an immunological response which is usually entirely unrelated to the presenting problem Since practically all children are soon exposed to common respiratory and pyogenic organisms positive reactions are the rule except in infants

Dietary Trials —Another approach in the attempt to establish an etiologic diagnosis with regard to food factors may be made by means of the trial diet the elimination diet or the food diary

Only rarely is it possible to obtain even a suggestive history of a flare up of the skin following the ingestion of certain foods More often the mother is bewildered by the relative inconsistencies she has observed Many different foods may be suspected yet the response may vary When foods are suspected as being important in the causation of allergic dermatitis a basic nonallergic diet would be a most helpful therapeutic measure Unfortunately no one such diet is perfect the responses are so highly individual that a relatively hypoallergenic food may produce reactions in certain cases If the child developed his eczema during the first few months of life and has never been off a cow s milk formula it is a relatively simple procedure to withdraw this food or modify its allergenicity by heating one hour in a double boiler

As previously mentioned it seems more rational to use either a soybean *preparation a meat base formula or Nutramigen* rather than goat s milk These are perfectly adequate foods on which growth and development are readily maintained

Depending upon the age of the child the basic diet usually consists of one meat one vegetable one cereal one fruit and synthetic vitamins It cannot be too strongly stressed that the caloric intake of the child must be carefully watched so that adequate growth may be maintained The basic diet most widely used consists of lamb rice pear and string beans It is based upon purely empirical findings and is certainly not effective in every case

If clear cut differences have not become manifest by approximately three weeks after the introduction of such a diet it is unlikely that further change will take place if the diet is continued Improvement in these children is not

only manifested by improvement in the appearance of the skin but also by a decrease in pruritus and often significant change in disposition with decreased irritability and much improved sleeping habits

After a suitable period of observation in cases which improve new foods may be introduced at five day intervals Each added food should be given daily in adequate amounts so that any change in the dermatitis will become evident If after five days of daily ingestion no change is observed it is unlikely that it will do any harm in the future

If during the time that the patient is on this restricted diet other forms of treatment are being used simultaneously improvement may not be wholly due to the dietary restriction alone It is therefore advisable when for example improvement has followed avoidance of milk to reintroduce milk into the diet and observe any changes which occur In clinical studies it has been our practice to repeat this procedure on two to three occasions in order to establish a definite cause and effect relationship between the patient s improvement when milk is eliminated and the exacerbation which follows the addition of this food to the diet

Infants on such diets should not receive mixed foods such as mixed vegetables mixed soups and complex cereals as any reaction attributed to such mixtures makes it difficult to evalute the actual cause It is always well to introduce a single food at a time so that any response can be clearly related There is no special order in which foods should be introduced As a rule we prefer to introduce wheat after other cereal grains have been tried and also to withhold egg until the child s progress is entirely satisfactory and he is at least a year of age Infants with atopic eczema are rarely allergic to meats and these excellent sources of protein rarely need to be withheld

The food diary is not very helpful in the study of allergic dermatitis unless there is a history of fairly regular periodic remissions and exacerbations It is based on the idea that review of a careful and detailed history of the child s diet may in retrospective examination reveal a possible relationship between the ingestion of certain foods and exacerbation of his dermatitis The mother is asked to keep a record of all foods ingested at each meal with approximate amounts and also note the general behavior of the child and the appearance of the rash This method of study has little application during the infantile period but may be of some use in the older child or adolescent

SPECIFIC TREATMENT

Foods —Specific treatment in any allergic disorder is based either on elimination or immunization For practical purposes immunization with foods is rarely successful (see Chapter 10 for details) Foods which have been proved by clinical trial to be important as causes should be eliminated It should be noted that many of these sensitivities decrease markedly or are lost completely with age For example it is not unusual for the infant who is highly sensitive to milk at 6 months of age to be able to take milk by the time he is 2 or 3 years old The dietary restrictions must be continued for several months after the rash is completely cleared but are not expected to be permanent

Milk substitutes are discussed in Chapter 8 These usually are well tolerated and are *nutritionally entirely suitable for maintaining good health* and growth Ordinarily little trouble will be experienced if soybean preparations are not given in full isocaloric amounts initially but are first given in a somewhat more dilute form and gradually increased in concentration Some of the infants develop loose foul stools and sore buttocks The manufacturers of milk substitutes are studying this problem attempting to discover if this is due to some step in the manufacturing process Very occasionally a milk sensitive infant may also be found to be allergic to beef and unable to tolerate formulas using this source of protein

The other foods offer less of a replacement problem than milk but if problems are encountered much helpful advice may be found in the books by F E Sammis *The Allergic Patient and His World* and M L Conrad *Allergy Cooking A Guide With Menus and Recipes* Both of these books are suitable for use by the mother in planning actual menus within the limitations set by the physician

Inhalants—Dust feathers pollens mold spores and animal danders have been noted as possible causative factors in the development of allergic dermatitis Many of these eczematous children give positive skin tests of the immediate type when tested with these substances Even though it may not be possible in most cases to demonstrate a clear cut relationship between the inhalant reactions and the dermatitis it is important to remember that many of the children with this disorder will subsequently develop nasal and respiratory allergies so that for prophylactic reasons contact with such allergens as dust feathers animal danders etc should be minimized as much as possible Occasionally a patient will be seen with a clear cut history of aggravation of skin symptoms following close contact with a dog or a cat

With respect to injection treatment with inhalants one can only state that injections of dust animal danders molds etc are used but their precise place in the treatment of allergic dermatitis cannot be stated at this time Many children receiving such treatment improve but since it is usually given concurrently with other forms of treatment evaluation is *difficult Such* treatment follows the general methods outlined in Chapter 10 but dosage should be conservative

Infection—It has been noted that during the course of respiratory infection and tonsillitis there may be an associated flare up of the skin rash In older children who have been followed over a period of time in whom this apparent relationship between infection and exacerbation of the skin has been noted and in whom the tonsil and adenoid tissue has appeared to be a focus of chronic infection remarkable sustained clinical improvement has been noted occasionally following operative removal of the infected tissue It is to be noted however that we do not advocate this as a routine measure in the *treatment of allergic dermatitis It is only in the selected case* who has been subjected to careful study and in whom this possible relationship between infection and aggravation of skin symptoms has been clearly demonstrated that operation should be considered Intensive treatment with antibiotics in these

instances has not yielded the same results This may be due to the fact that a certain number of resistant organisms may survive in the tissues so that complete sterilization is not possible

In cases of atopic eczema where infection is believed to be a factor infections of stock or autogenous vaccines are often used in accordance with the methods outlined in Chapter 10 Since this form of treatment is usually combined with other types of therapy evaluation of the benefits derived from it is difficult When the causative infection is susceptible of surgical treatment as by tonsillectomy the latter is usually more effective than vaccine treatment

The treatment of secondary infection of the skin lesions is discussed in the following section

SYMPTOMATIC TREATMENT

Support for the Entire Family—It is extremely important to remember that one is dealing with an acutely distressing condition which is not only troublesome to the patient but involves the entire family There is nothing more disturbing to the mother with a six months old baby who has not slept for the past month than to be told that nothing can be done now that by the time the baby is a year or two old he will have outgrown this condition It is important to explain the disease and its natural history to the parents indicating that it is not a hopeless situation by any means that effective treatments are available that scarring will not result and that secondary infection is rarely serious Such reassurance and sympathetic understanding in handling the family are a great help in treating this condition

Prevention of Mechanical Trauma—This often is more difficult in practice than it sounds In the young infant elbow restraints and keeping the arms and legs covered either with white laundered socks or cotton tubular bandage help to some extent in decreasing the amount of scratching that the child does and the amount of harm that is produced The nails should be cut short Often placing the patient on a smooth plastic sheeting and avoiding contact with rough or irritating materials will be of some benefit Wool contact is to be avoided

Occasionally exposure of the skin to the atmosphere without any contact with shirt or diaper will also help in skin healing In order to minimize exposure to drafts the crib may be lined with cotton blankets and a heating lamp placed over the crib so that the skin may be kept warm Care must be taken that the baby not be burned nor be able to touch the lamp

Mechanical restraint has been opposed because of the fear of the psychic trauma induced by such a device In the baby with severe pruritus it is almost impossible to devise any form of restraint which is effective Its use in the hospital is occasionally necessary because of a shortage of nursing personnel to handle the baby At home elbow restraints and keeping the baby clothed are much more satisfactory measures especially since with attention and diverting his interest scratching may often be lessened

Sedatives and Antihistamines—Although sedatives are strongly recommended in the treatment of atopic dermatitis both of infants and older chil

dren in practice they often present a problem in securing the desired results The usual pediatric doses are often ineffective and one hesitates to use large amounts of sedation over a protracted period of time The dose of 30 mg of phenobarbital three times a day rarely produces a therapeutic effect Seconal or Nembutal 60 mg as a rectal suppository may be given at bedtime for a few days but not continued over a period of weeks The tranquillizing agents have on the whole proved disappointing in children with severe pruritus Hill in his excellent book on the treatment of eczema has recommended chloral hydrate *

As a rule antihistamines are not very effective in controlling the pruritus When they do it is usually because of their sedative side effect It is worth while to try the more sedative drugs of the group for a period of time but their continued use in the absence of any real effect is contraindicated

Wet Dressings —During the acute active erythematous weeping stage wet dressings are most helpful Aluminum acetate (Burrow s solution) diluted 1 20 is readily available does not stain and appears to be as effective as any other form of wet dressing Used intermittently three or four times a day for twenty to thirty minutes at a time it often produces considerable relief When it is used as a continuous wet dressing the skin should be examined frequently so that maceration of the tissue will not occur

This type of preparation is effective during the acute phase in reducing the amount of weeping and erythema of the skin After its use the skin should be bathed but not rubbed dry and any other medication applied

In addition to aluminum acetate potassium permanganate saline and other solutions have been recommended in the treatment of this acute phase of allergic dermatitis It is much more reasonable to concentrate on the use of one medication than to try a variety since there seems to be little difference in the efficacy of one form of wet dressing as compared to another in this disease

Coal Tar Derivatives —Over the years coal tar has been widely used in the treatment of the subacute and chronic phase of infantile eczema It may be used in concentrations of from 3 to 5 per cent in Lassar s paste or zinc oxide ointment and a variety of proprietary preparations† are available Occasionally their use is followed by considerable improvement in the skin They are inexpensive but may have a tendency to make the skin turn dark The material should be washed off before the child is exposed to sunlight as they are active photosensitizing agents ‡

Topical Hydrocortisone —Hydrocortisone 1 to 2 per cent or prednisolone ½ per cent in a light ointment base or lotion has been found to be very effective in the treatment of allergic dermatitis Its topical use is not associated with any significant side effects In a case of generalized eczema prolonged use often becomes prohibitive because of the expense involved While it is quite

* Noct [illegible] solution (5 ml contain [illegible] 500 mg) [illegible]
† For example [illegible] Supe[illegible]
‡ [illegible] tion appl[illegible] to the [illegible] (for 24 hours) [illegible] to be [illegible] the patient shows no peculiar [illegible] orable reaction to the med[illegible]

effective at first not infrequently it seems to lose its effect with continued administration It is particularly useful during the initial treatment when a patient is being studied in an attempt to find specific causes for his eczema Initially it must be used several times a day in order to get a good effect It may be worth while to use it at first only on a section of the body and try another less expensive preparation on the other side and compare the results When used in this way one not infrequently notes that other less expensive preparations are equally effective

Systemic Steroids and Corticotropin—Cortisone and related agents are palliative and not curative Where possible they should be used systemically only after all other forms of therapy have been tried and found to be ineffective When the patient and his family are thoroughly depressed because of the failure to improve these agents may give new hope They are preferably to be used over a short period of time perhaps not more than ten days to two weeks in the minimal effective doses Prednisone and prednisolone in amounts of 15 to 20 mg as the initial 24 hour dose have proved to be effective in the pediatric age group This dose is rarely maintained for more than 48 hours and is decreased by 2 5 to 5 mg amounts during the succeeding days depending upon the clinical state of the patient Cortisone and hydrocortisone are equally effective but more apt to produce fluid retention The various side effects are discussed in Chapter 4

These drugs have been of considerable help in treatment of the acutely distressed child It cannot be stated too strongly however that they give a false sense of security They are potent agents and in dealing with a growing organism their use as a routine measure for the treatment of this disorder cannot be accepted

Corticotropin has of course the disadvantage that it must be given by parenteral injection When effective the response appears to be more rapid than that of the corticosteroids Injections of 30 to 40 units are usually required as initial doses

The Use of Baths—No blanket statement can be made regarding bathing these children In some instances the mere sight of the bathtub will distress the eczematous child so that it is almost impossible to put him into the tub If the child is fearful of a bath the skin should be carefully cleaned by sponging Other children on the contrary will like a bath In some cases the pruritus seems to become more marked as a result of bathing

Baths are necessary to remove the thick crusts from the oozing weeping skin in order to expose the affected areas to the medication which is used topically The lotions or ointment put on these crusted areas are largely ineffective Using a detergent such as pHisoderm Lowila or Dermolate will aid in removing the crusts Soap is usually poorly tolerated

Colloidal baths using starch oatmeal or proprietary preparations (Aveeno) have been used In some cases they allay or decrease the itching In others they seem to do little good They usually tend to dry the skin so that in those cases where the skin is already dry and flaky they seem to aggravate this condition

Clothing—Direct contact with silk and wool is to be avoided even though the skin tests for these allergens are negative. The clothing should be of smooth soft fabrics and should be kept thoroughly clean.

Secondary Infection—Because of scratching secondary infection is often present in acute eczema. In the treatment of these cases systemic administration of chemotherapeutic and antibiotic agents in full doses is often to be preferred to topical application. *It is a common observation that the frequency of sensitization following the topical application of penicillin to eczematous skin is so high that there is little justification for its use.* In various series this undesirable complication has been reported to occur in 5 to 10 per cent of patients. *Though some of the other antibiotic agents do not cause as much contact sensitization* considerable care must be taken in their use. Some of these such as polymyxin and bacitracin have toxic properties if used by systemic routes. In an infant with a widespread area of denuded skin it is not inconceivable that enough absorption may occur through the skin so that unexpected complications may occur from extensive and persistent topical use of these agents.

Hospitalization—As a rule hospitalization for eczema is not desirable. In the hospital where there may be exposure to a variety of different infectious agents the possibility of cross infection exists. This has become less important since effective antimicrobial agents are available. For proper symptomatic treatment a great deal of time is needed and it is well to be sure that adequate nursing care will be available. However in order that potent agents may be used promptly that the patient may be watched carefully to enable the physician to obtain much data in a brief period of time and also that the family may obtain some rest hospitalization may be desirable and produce prompt and dramatic results.

PROGNOSIS AND COMPLICATIONS

The majority of cases of infantile eczema show clear normal skin by the time the infant reaches 18 months to 2 years. As a rule there is no scarring and the skin retains its smooth normal texture. A significant group of patients have by this time developed respiratory allergy and must be treated for this condition. A small percentage of patients continue to have allergic dermatitis into later childhood and even adult life. *These chronic cases are apt to develop* persistently rough and thickened skin. It is impossible to predict which case will fall into any given category so that if the child has persistent symptoms of the disease effective treatment should be directed along the lines of symptomatic relief as well as an unravelling of possible causative factors.

Generalized edema is fortunately no longer a frequent complication of infantile eczema. When it occurs it is usually due to loss of serum proteins through the weeping oozing skin or the loss of keratinized material from the skin but may also be due to too restricted a diet maintained over too long a period of time or to anorexia vomiting or profuse stools.

Kaposi's varicelliform eruption is an acute vesicular dermatitis associated with fever and often severe constitutional symptoms affecting children with

atopic dermatitis It is believed to be due to infection of the atopic dermatitis with the virus of herpes simplex Care should be taken to avoid exposure of eczematous children to patients with herpes simplex in order to avoid this serious complication Once the condition develops treatment is supportive Antibiotics are not effective against the herpes virus but may be helpful if secondary pyogenic infection occurs

Children with eczema must not be vaccinated against smallpox nor may they be permitted in contact with anyone who has recently been vaccinated They are highly susceptible to infection with cowpox virus which spreads rapidly on the eczematous skin producing a serious and occasionally fatal illness Children who survive are apt to be severely scarred

During the management of patients with eczema it is important that they receive the immunizing agents other than smallpox vaccination which are used in this age group Reactions to diphtheria and tetanus toxoid and pertussis vaccine are rarely seen and these agents should be administered in the same manner as they are given to the noneczematous child It is important that their immunity be kept at a high level with booster shots at approximately two- to three-year intervals

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Chapter 14

URTICARIA AND ANGIOEDEMA

Definitions.—*Urticaria*, also spoken of as hives or nettle rash, is a skin eruption composed of sharply defined flat areas of edema of the skin surrounded by erythema. *Angioedema*, also called angioneurotic edema or giant urticaria, is a more extensive circumscribed swelling similar to the lesion of urticaria but involving the subcutaneous tissue as well as the skin. It may occur as an isolated lesion or in conjunction with simple urticaria. *Dermatographism* is a condition in which stroking or scratching the skin with a blunt instrument causes the formation of an urticarial lesion at the point of contact, such lesions being called *urticaria factitia* (see Chapter 22).

URTICARIA

Etiology

Most cases of urticaria occurring in children are allergic in nature, this age group being less susceptible than adults to chronic urticaria of obscure etiology. The eruptions are characteristic manifestations of both the atopic and anaphylactic types of sensitization and may occur either as the sole evidence of an allergic reaction, or as a part of a generalized reaction such as serum sickness or the constitutional reaction to the injection of an excessive dose of an antigen. Children with the hereditary tendency to atopic sensitization indicated by the presence of other atopic diseases in the patient or his family are peculiarly susceptible to urticaria due to foods and other naturally encountered allergens, but the occurrence of urticaria after the injection of heterologous serum or penicillin is not notably related to hereditary factors. Heredity has been stated to be a factor in 22 to 28 per cent of cases of urticaria in all age groups, but the *proportion in children is undoubtedly higher.*

The causative agents producing urticaria are many and varied including foods drugs sera and other biologic products contact agents parasites bacterial infections and physical agents In patients rendered susceptible by such specific causes attacks may be produced or lesions brought out in particular locations by nonspecific factors which irritate the skin or increase the flow of blood to it such as heat scratching exertion tight clothing or emotional stress

Foods are the commonest causes in infants and children Almost any food may be the causative agent in an occasional case but the commonest offenders are eggs fish shellfish raw fruits particularly berries chocolate nuts pork and milk Foods that are eaten only occasionally or that have recently been added to the diet are more apt to cause hives than those taken habitually In most cases the eruption appears within a few hours after eating the causative food but occasionally its onset may occur within a few minutes or be delayed for twelve to twenty four hours The reaction time of successive attacks due to one antigen in the same child is usually fairly constant

Among drugs the list of possible offenders is also very long At present penicillin is by far the commonest offender in this group with the onset most often delayed a week or so after the first dose as a part of the serum sickness type of reaction but occasionally occurring almost immediately as a part of the anaphylactic type of reaction Other drugs which are among the more frequent causes include aspirin and other salicylates the sulfonamides barbiturates and codeine The occurrence of urticaria as a manifestation of serum sickness or of an immediate reaction to heterologous antiserum has been described in Chapter 6 Other biologic products containing foreign protein such as insulin vaccines and toxoids may cause immediate reactions but less often than heterologous antisera

Contact agents are among the less frequent causes The saliva of a pet dog or cat licking the skin may produce hives Silk particularly in its less highly finished forms may be a specific cause Wool in contact with the skin may be a specific cause but more often acts as a mechanical irritant bringing out lesions due basically to some other cause The possibility of its resulting from contact with nettles (Urtica) gives urticaria its name Plants of this genus are covered with bristly hairs which contain a toxin that produces hives in nonsensitized skin This material is a primary urticariogenic agent rather than an allergen

Parasitic worms of various types may cause urticaria as a manifestation of anaphylactic sensitization to the parasite in the tissues The usual reaction of the skin to bites of mosquitoes bedbugs fleas and other insects resembles a small hive but in sensitized children these bites may produce large and typical urticarial lesions Occasionally multiple bites in a highly allergic child may cause generalized hives with lesions appearing elsewhere on the body Typical urticarial lesions are also occasionally seen as reactions to scabies and pediculosis

Bacterial infections which are a major cause of chronic urticaria in the adult less often play a similar role in children

Physical agents may be a primary cause of urticaria as a manifestation of physical allergy or may act as nonspecific precipitating factors in urticaria due to other causes As primary etiologic agents cold light and occasionally heat

may produce urticaria Heat particularly a hot bath is a frequent precipitating factor in urticaria due to other causes because of increased blood flow to the skin Mechanical pressure and friction tend to bring out latent urticaria in areas where the skin is scratched or the clothing is tight

Emotional factors are less important causes of urticaria in children than in adults but occasionally act as precipitating factors producing attacks in children made susceptible by other causes

Physiology and Pathology

The urticarial wheal is readily reproduced in nonallergic skin by the injection of histamine or histamine liberators and naturally occurring hives are usually inhibited by adequate doses of antihistamine drugs For these reasons and because of the analogy to other anaphylactic and atopic reactions the occurrence of urticaria is generally attributed to liberation of histamine as a result of an antigen antibody reaction or less often through some other mechanism In most cases of acute urticaria no measurable change of the plasma histamine is demonstrable but in cases of severe cold urticaria the systemic circulatory and secretory effects of histamine have been noted after local application of cold to an extremity In certain patients with urticaria derivatives of acetylcholine have been shown to produce wheals in the skin Possibly acetylcholine plays some part in the production of naturally occurring urticaria however its pharmacologic antagonist atropine has no significant therapeutic effect in contrast to the efficacy of antihistamine drugs

Histologically the urticarial wheal consists chiefly of edema of the corium most marked in the subpapillary zone The blood vessels and lymphatics are dilated and there is mild infiltration of lymphocytes and polymorphonuclear leukocytes including a few eosinophils

Symptoms

The typical urticarial lesion or wheal is a discrete flat swelling of the skin with a sharply defined margin The actual wheal may be blanched or red the surrounding area is diffusely red Individual wheals vary in size from a few millimeters to 10 or more cm in diameter The smaller lesions tend to be round but the larger ones which presumably result from coalescence are irregular in outline In infants the typical raised border is less definite the lesions are slightly elevated reddened areas which may merge into large areas of erythema

Itching of the lesions is usually marked Often the itch may precede the appearance of a visible wheal and if the skin is scratched the lesions tend to develop in a linear form Because of the itching and scratching excoriations and secondary infections of the skin are not unusual

The individual lesions are relatively transitory usually lasting only a few hours Those that persist longer lose their sharp outline and remain as elevated erythematous spots Successive crops of lesions may appear in the same or other areas of the skin No portion of the skin is immune but the palms

soles and scalp are less often affected The most typical lesions are on the relatively flat areas of the body arms and legs When the hands feet face and genitalia are affected the swelling is usually diffuse and assumes the form of angioedema Involvement of the tongue pharynx and larynx may occur with serious danger of asphyxia occasionally requiring a prompt tracheotomy

When urticaria occurs as part of a general allergic reaction rhinitis asthma *and gastrointestinal and cerebral symptoms may also be present* The gastrointestinal and cerebral symptoms which sometimes occur with such reactions are believed to result from internal urticarial edema of these systems a view which has been supported by operative findings in cases where exploration was considered necessary

The duration of an attack of urticaria varies from a few hours to several weeks Chronic cases are far less common in children than adults The duration depends chiefly on the cause and whether there is continuing contact However in certain cases due to penicillin the symptoms may persist for weeks after the last injection

Diagnosis

In its typical discrete form the urticarial wheal is usually easily recognized Very extensive confluent urticarial rashes may be less distinctive in appearance but the characteristic raised margin can usually be seen in some areas during the acute stage If the erythematous skin is gently stretched the raised edematous areas blanch and stand out clearly from the surrounding reddened areola

Differentiation of hives from insect bites is usually possible since the latter tend to occur in groups over exposed portions of the body and typically progress to papular or vesicular lesions As previously noted children allergic to insect allergens may develop large and typical urticarial wheals at the site of the bites during the first few hours Even at this stage the central bite may be visible The difficulty in differentiation that may be encountered in some cases is reflected in the diagnosis of *papular urticaria* or lichen urticatus which has long been described as a distinct form of urticaria in infants and children but is now believed to result from insect bites These lesions appear in crops chiefly at *night with the appearance of small urticaria which persist as itching* papules The arms and legs are chiefly affected but the face may be involved Skin tests with mosquito and bedbug antigens have been shown to produce positive reactions in a large proportion of cases The most successful therapy is based on the use of insecticides insect repellents and similar protective measures Differentiation of this condition from urticaria due to other causes depends on the appearance of the more advanced lesions their distribution and the presence of insect bites in other members of the family

Urticarial wheals may also occur in allergic children infested with scabies or pediculi Diagnosis depends on the demonstration of the parasites or in scabies of the typical burrows The presence of itch without urticaria in other members of the family is also suggestive

Simple urticaria should also be distinguished from *urticaria pigmentosa* a relatively chronic rare skin disease of infants and children This is character

ized by lesions over the body and extremities which at first have the appearance of typical urticarial wheals However the individual lesions persist for several days or weeks and when they subside leave persistent spots of brownish pigment After a few weeks the appearance of the eruption is very characteristic The etiology of urticaria pigmentosa is unknown but there is no evidence that allergy is involved

Dermatographism is closely related to simple urticaria Most patients with acute urticaria exhibit dermatographism during the attacks the lesions often appearing in areas where the clothing is tight or where the child scratches However certain children have persistent or permanent dermatographism for which no specific allergic cause can be demonstrated In these cases linear urticaria may be produced at any time by friction This has been classed as a type of physical allergy but evidence of an immunologic mechanism is lacking

Diagnosis of the Specific Cause —In determining the causative factor a careful history is essential noting particularly any relationship of the attack to changes in diet oral or injected medications clothing or activities Physical examination should include a careful search for infections especially of the upper respiratory system In persistent cases the stool should be examined for parasites

If a food is suspected and the attack follows within a few hours after ingestion confirmation by means of skin tests is usually possible If the urticaria is part of a general allergic reaction the initial test should be a scratch test Intracutaneous tests may be done cautiously if the scratch test gives little or no reaction The initial intracutaneous test with the suspected food should be done with a tenfold or one hundredfold dilution of the routine testing strength One should remember that the antigens of shellfish and berries both common causes of acute urticaria are exceedingly unstable so that extracts prepared by the usual techniques rapidly become impotent A scratch test with the fresh or frozen material may be more reliable than an intracutaneous test with the usual extracts If the attack follows four or more hours after ingestion of a specific food the skin tests are usually negative

Because of the difficulties in skin tests with foods many physicians omit them and rely entirely on elimination diets for diagnosis However observation of the effects of trial diets is necessarily a prolonged and tedious procedure while skin tests in many cases give an immediate answer It therefore seems wise to do a reasonable number of skin tests on children of 4 or older whose urticarial wheals are suspected of being due to foods but if the reactions are not consistent with the history to resort to trial diets eliminating the most common offenders and any additional foods which are suspected seems best

Skin tests with penicillin are rarely diagnostic except in immediate reactions and tests with synthetic drugs involve risk out of proporton to the results obtained (see Chapter 21)

Treatment

If the child is seen on the first day of acute urticaria and there is no obvious cause other than a food a saline cathartic should be given to clear

the gastrointestinal tract of any possible allergen In very severe attacks associated with generalized manifestations of allergy to food gastric lavage or an emetic may be advisable during the first few hours Unless there is presumptive evidence of a cause other than food the diet should be temporarily restricted to avoid the foods which most often cause urticaria namely eggs pork chocolate raw fruits nuts spices fish and shellfish

The most useful drugs for the treatment of acute urticaria are the antihistamines Any of these may be given in the usual doses and repeated once after one half to one hour if necessary Subsequent doses may be given every four to six hours as needed If the child is restless one of the more powerful and sedative drugs such as Phenergan or Benadryl is preferable Although the antihistamine drugs are readily adsorbed from the digestive system intramuscular injections sometimes seem to give better results than oral administration

If the attack is accompanied by symptoms of a generalized allergic reaction or if the tongue and throat are edematous epinephrine 1 1000 0 1 to 0 4 ml intramuscularly should be given and repeated as necessary Once the condition is controlled relief may be sustained by the use of epinephrine in oil 0 3 to 1 0 ml intramuscularly For mild attacks ephedrine sulfate 10 to 25 mg by mouth may be helpful as a supplement to antihistamine therapy

For prolonged severe attacks which do not respond well to antihistamines particularly those due to antiserum or penicillin which also involve other organs than the skin cortisone prednisone and corticotropin are useful The dosage must be adjusted to the severity of the reaction but after relief is obtained usually in one or two days may be rapidly decreased and the drug stopped after 4 to 6 days

In most cases of urticaria local applications for the relief of itching are useful adjuncts to systemic medication and in mild cases they may suffice for the sole treatment Calamine lotion with 1 per cent phenol or various proprietary modifications of this mixture may be applied freely Wet dressings with sodium bicarbonate and starch baths are also helpful

Avoidance of the cause is obviously essential to the prevention of recurrent attacks However the amount of study and restriction of diet which is considered necessary will depend on the number and severity of attacks and the age of the child Review of the diet and medications preceding the onset is always indicated If a single mild attack has occurred simple advice to avoid a suspected food may suffice More severe and repeated attacks justify a definite attempt to establish the cause by skin tests trial diets and other procedures

Prognosis

Urticaria is dangerous only in those cases where edema of the tongue mouth and larynx occurs or in which the skin rash is only one manifestation of a systemic allergic reaction The duration of the attack of simple urticaria and the probability of recurrence depend on the nature of the exciting cause and whether it can be avoided Attacks due to foods usually subside in a day or two after ingestion is stopped those due to most drugs are equally brief but in the case of penicillin occasionally may last for weeks or even months

ANGIOEDEMA (GIANT URTICARIA)

Symptoms

Angioedema is similar in pathogenesis and causative agents to urticaria but the swellings are larger and involve the subcutaneous tissues as well as the skin The term angioedema is preferable to the older one angioneurotic edema since the latter implies a psychosomatic mechanism rarely if ever present in children The face ears hands feet and genitalia are most often affected The swellings are firm nonpitting on pressure and fairly sharply defined but without the raised border seen in simple urticaria The overlying and surrounding skin usually shows little or no erythema except when the angioedema is a part of a systemic allergic reaction Simple urticaria may or may not be present in other areas The subjective symptoms are mild with a feeling of tension rather than itching or pain Involvement of the tongue uvula and larynx may occur and represent a serious threat of asphyxia The swellings usually persist only for a day or two but may recur in the same or different locations

Diagnosis

The diagnosis is based on the circumscribed nature of the swellings the absence of pain and inflammatory signs and the lack of fever Careful examination of the adjacent structures (for example the teeth in swellings of the face) for infection is essential While recurrence of angioedema in the same or different areas is common persistent swelling of one area which does not completely subside over a period of weeks or months is almost invariably due to other causes such as lymphedema In doubtful cases a trial of treatment with suitable drugs may help to establish the diagnosis

Treatment

If the tongue uvula or larynx is involved the treatment is urgent because of the danger of laryngeal obstruction Epinephrine 1 1000 0 1 to 0 5 ml intramuscularly may be given every ten minutes for four or five doses if necessary and supplemented with one or two intramuscular injections of Benadryl 10 to 20 mg or Chlor Trimeton 5 to 10 mg Treatment with corticotropin intramuscularly or by intravenous infusion may be started concurrently With actual edema of the larynx evidenced by hoarseness and stridor preparations should be made for a prompt tracheotomy in case of further obstruction If the swelling is controlled with aqueous epinephrine and antihistamine drugs epinephrine in oil 0 3 to 1 0 ml is given to prevent relapse Cortisone or prednisone may also be started

Angioedema of other portions of the body or face is treated by the measures applicable to simple urticaria As local applications iced compresses may be helpful

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Chapter 15

GASTROINTESTINAL ALLERGY

Gastrointestinal allergy refers to the manifestations of sensitization of the alimentary tract as a shock organ. The great majority of such sensitizations are due to foods, a few to drugs, but the category is to be distinguished from that of food allergy, which may also affect various other organs of the body with such reactions as rhinitis, asthma, and urticaria.

ETIOLOGY

The allergies of the gastrointestinal tract are usually of the atopic type and affect chiefly children whose families have diseases of this group or who themselves have been affected by them. Practically any of the foods eaten by children may occasionally cause such reactions. Cow's milk is the most often suspected cause because of its prominent place in the diets of infants and children. Eggs, wheat, corn, chocolate, fish, shellfish, and chicken are other common causes. The meats are only rarely significant causes.

PHYSIOLOGY

The reactions of gastrointestinal allergy vary from the violent immediate type which follows within a few minutes after eating a highly allergic food and in which the relationship to the specific food is usually very obvious, to chronic disorders which may be delayed some hours after ingestion of the food so that the casual relationship of foods is difficult to determine. The physiologic changes in the gastrointestinal tract are similar to those of the immediate type of allergic reaction in other organs: edema, spasm of smooth muscle, and increased secretion of mucus.

Fries and others have described the roentgen changes in the gastrointestinal tracts of children 3 to 12 years of age when given the specific allergic food mixed with barium either by mouth or as an enema. Comparisons were made with studies on the same children using plain barium and barium mixed with foods to which they were not allergic. The changes were most frequently noted in the stomach, with delayed emptying the chief feature. In most cases there was a 15 to 50 per cent retention at six hours. Changes in the small intestinal pattern, usually segmentation of the barium column, were noted less often and chiefly in children with the most severe symptoms. Hypermobility of the colon was also noted in some cases. When the allergen barium mixture was given as an enema, spasm of the transverse and descending colon was seen in about half of the patients. Care is essential in interpreting such studies since it has been shown that the emotional distress caused in a child by the unfamiliar procedures of fluoroscopy, the barium meal and the contrast enema may itself produce changes not unlike those produced in the allergic child by the allergenic food. This psychic factor must be ruled out for significant results.

SYMPTOMS

The acute type of reaction to a food to which the child is highly allergic is often manifested within a few minutes after ingestion. Itching, burning and edema of the buccal mucosa may be almost immediate and followed quickly by vomiting and diarrhea. The gastrointestinal symptoms may be only part of a general reaction involving the skin, respiratory system and circulation with urticaria, asthma and vasomotor collapse. Such reactions are most often caused by eggs, nuts, fish, shellfish, buckwheat and cottonseed flour used in commercial doughnuts.

The symptoms commonly associated with the less acute reactions are usually vomiting, abdominal cramps, abdominal distention and diarrhea. The latter may be associated with considerable amounts of mucus in the stools and occasionally, especially during infancy, frank blood. Secondary effects may also be noted, such as irritability, lassitude or failure to gain weight because of loss of food in the vomitus and stools. The buccal mucosa is less often affected in the chronic than in the acute reactions. These are the gastrointestinal symptoms which are often related to food allergy with considerable certainty. Many others have been attributed to it in occasional cases or on questionable evidence.

Many of the gastrointestinal diseases of obscure etiology, including aphthous stomatitis, hypertrophic pyloric stenosis, the celiac syndrome and chronic ulcerative colitis, have been attributed by various writers to food allergy. In occasional cases of aphthous stomatitis and celiac syndrome a relationship to food allergy has apparently been established, but the number of such cases is small in relation to the frequency of these syndromes. In regard to hypertrophic pyloric stenosis and chronic ulcerative colitis, the symptoms of these conditions may be simulated by gastrointestinal allergy, but evidence that their complete pathologic pictures are produced by this cause is not conclusive.

DIAGNOSIS

The severe immediate type of gastrointestinal allergy usually presents no diagnostic problem Both the allergic nature of the reaction and the causative food are obvious in most cases

On the other hand the delayed and chronic types may be difficult to recognize The diagnosis is suspected when the symptoms mentioned above occur in a child who has previously shown manifestations of other atopic diseases or has a strong family history of such disease Other causes for the patient s complaints such as bacterial and virus infections of the gastrointestinal tract congenital malformations strictures and bands deficiencies of pancreatic or other digestive enzymes etc must be considered and ruled out

Proof of the diagnosis must be based almost entirely on clinical observation and dietary trials The case history will help to limit the number of foods to be suspected Unfortunately skin tests both direct and indirect do not often yield significant results except in the severe immediate reactions where the diagnosis is easy without their aid The basic consideration must rest on the clinical pattern which follows the removal of the offending agent from the child s diet or environment and its deliberate reintroduction If it can be demonstrated on two or three occasions that clinical improvement follows the elimination of the offending food and that a flare up follows promptly on the introduction of the allergen into the diet then the diagnosis can be entertained with some degree of assurance

During infancy cow s milk is incriminated more frequently as a possible cause of gastrointestinal allergy than all other allergens combined The fact that a baby s symptoms are ameliorated or eliminated completely following the removal of milk from his diet is satisfying but is not proof of a cause and effect relationship The addition of milk to his diet must again reproduce the symptoms which were eliminated when milk was removed Not all changes resulting from dietary restrictions are indicative of allergy for example the effects on cœliac syndrome of eliminating starches or fats

The diagnosis of gastrointestinal allergy is made much more frequently than it is proved This does not mean that repeated attempts to cause recurrences are necessary or desirable in every child who improves after a change of diet but the physician should understand the difference

A variety of other laboratory aids intended to be useful in making this diagnosis have been proposed On the whole most of these are either not rewarding or are cumbersome so that their clinical usefulness is limited

Examination of the stools for the presence of eosinophils has been suggested When they are present they are usually found in stools containing considerable amounts of mucus We have not found this technique particularly helpful and have not seen stool eosinophilia with any frequency

Such procedures as the leukopenic index or changes in blood pressure following the ingestion of a suspected allergen have likewise yielded inconsistent results Recently Black has reported a method using leukocyte survival time as an indicator for sensitization This method has as yet not been subjected to extensive use so that no conclusive statement can be made as to its usefulness

Roentgen studies with mixtures of barium and the suspected food may occasionally be helpful in diagnosis Their usefulness is limited by the nervous factors previously mentioned and they are not easily carried out on infants among whom gastrointestinal allergy is often suspected From the practical standpoint the time and expense involved in the control and actual studies must be considered Since only one food may be tested at a time the method lends itself more to confirmation of a suspected diagnosis than the initial survey

Most often the diagnosis is still established by carefully observing the effects of a logical plan of dietary changes

TREATMENT

Severe acute reactions require prompt treatment with epinephrine intramuscularly in conjunction with which injections of antihistamine drugs may be used This treatment which is that of any generalized atopic reaction is described in detail in Chapter 7

The less acute gastrointestinal reactions are treated primarily by elimination of the causative food The available substitutes for cow s milk in infant feeding are discussed in Chapter 8

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Chapter 16

ALLERGY OF THE EYE

Allergy has been proved to be the cause of a number of diseases of the eye observed in children and suspected as a factor in many other conditions of obscure etiology The allergic diseases affecting the conjunctivae and lids may reasonably be handled by the pediatrician or general practitioner Those affecting the interior of the eye are best diagnosed and treated by the trained ophthalmologist although the physician interested in allergy may be called upon to evaluate the presence of an allergic factor in their causation In these cases it is wise to remember that positive reactions to skin tests are not definite evidence of an etiologic relationship but rather clues which may be the basis of further study of an obscure case

ALLERGIC CONJUNCTIVITIS

Allergic conjunctivitis may be divided into three types (1) atopic (2) dermatoconjunctivitis related to contact dermatitis and (3) bacterial related to the delayed type of bacterial allergy

Atopic Conjunctivitis

The atopic type of allergic conjunctivitis is familiar as a feature of acute hay fever but may also occur without nasal symptoms Less often it may be one manifestation of an acute generalized allergic reaction to a food allergen If other allergic symptoms are not present simultaneously there is usually a past history of atopic diseases in the child or his family

The most common causative allergens are pollens although molds and other inhalants are not infrequent causes Foods are less often a factor

In the more acute cases redness and edema of the conjunctivae are the

striking features Introduction of considerable amounts of allergen as when the child rubs the eye with hands contaminated with allergen may cause marked chemosis Itching is severe and there is profuse tearing but no pus

In the chronic stage there is only slight redness and edema is rarely marked although the subjective symptoms of itching burning and dryness may cause considerable distress

Smears from the conjunctivae usually show a preponderance of eosinophils Cultures of the conjunctivae in general show no significant organisms These features serve to distinguish allergic conjunctivitis from infective types

Prompt relief is usually afforded by epinephrine and cocaine eye drops (Chapter 4) and the oral use of antihistamine drugs is quite effective Cortisone eye drops produce less rapid but more lasting relief

Skin tests with pollens molds and inhalants usually reveal the causative allergen by an immediate urticarial reaction Once the antigen has been determined the usual methods of avoidance or injection treatment are undertaken

Dermatoconjunctivitis

The contact type of allergic conjunctivitis is immunologically similar to contact dermatitis and is often accompanied by dermatitis of the eyelids In children it is most often due to sensitization to drugs applied to the eye as drops or ointments The various local anesthetics atropine penicillin and the sulfonamides are notable sensitizers among the commonly used medications This type of allergy is not related to the hereditary tendency to atopic diseases

The conjunctival reaction is papillary and edema is rarely marked The discharge is watery Eosinophils are present only in the chronic cases The lids are usually swollen with thickening redness and occasionally vesiculation of the skin Dermatitis of the lids due to eye drops tends to develop along the natural paths of the tear flow while that due to ophthalmic ointments tends to involve the lid margins

If the conjunctivitis results from a medication the diagnosis is usually apparent unless the allergic reaction be confused with an exacerbation of some pre existing condition The causative allergen is determined by the delayed reaction to a patch test (See Chapter 18)

Recovery follows removal of the cause and drugs are required only in the more severe cases The topical application of cortisone is the most effective remedy Antihistamines and vasoconstrictors are of little or no value in this type of allergic reaction

Conjunctivitis Due to Bacterial Allergy

The importance of sensitization to the toxin of the hemolytic *Staphylococcus aureus* as a factor in chronic conjunctivitis has been stressed by Woods and his associates This condition is apparently a manifestation of the delayed type of bacterial allergy and not related to atopy

The conjunctivae are reddened and rather dry without edema The discharge is watery The lid margins are swollen and red The subjective symp-

toms are burning and dryness rather than itching Eosinophils are not present in smears cultures usually show hemolytic staphylococci unless there has been active local treatment with antibiotics However because of the sensitization the conjunctivitis can persist after the culture is negative Children with this disease show a strong delayed reaction to intracutaneous tests with staphylococcus toxin Woods considers a large reaction to 0 1 ml of the 1 100 dilution significant of allergy

Symptomatic relief by drugs is not satisfactory Antihistamines and vasoconstrictors are without effect and cortisone is less effective than in most other allergies of the conjunctivae

Treatment entails elimination of the organism by the topical use of antibiotics and other antiseptics and desensitization by injections of staphylococcus toxin or toxoid The injections are given intracutaneously at weekly intervals starting with 0 1 ml of a 1 1 000 or 1 100 dilution and increasing gradually to 0 1 ml of the 1 10 dilution in accordance with the tolerance developed The top dose is repeated at intervals of one to four weeks for six months

VERNAL CONJUNCTIVITIS

Vernal conjunctivitis or vernal catarrh is a recurrent form of conjunctivitis common in children with exacerbations in spring and summer It has been suggested that this condition may be allergic in nature but definite proof is lacking

Etiology

The etiology must be considered unknown The condition appears to be more frequent in children with a family history of atopic disease but is not limited to this group Association with hay fever or other atopic diseases is frequent The seasonal incidence suggests the possibility of allergy to a pollen or mold but the season does not correspond to that of any particular pollen and the symptoms often persist after frost when atmospheric mold spores are rare Skin tests with pollens or other inhalants often show definite reactions but treatment by injections or avoidance of the reacting allergens is not effective Presumably these reactions reflect an associated atopic constitution and not specific causative factors in the conjunctivitis

The condition is more common in boys than in girls and often but not always improves at the time of puberty These facts have suggested the possibility of an endocrine factor but no definite evidence of its nature is known

Symptoms

The appearance of the conjunctivae is characteristic with flattened papules on the tarsal conjunctivae especially of the upper lids usually described as resembling cobblestones edema of the limbal conjunctivae and redness of the bulbar conjunctivae Itching is usually rather severe There is a thick white tenacious mucoid exudate which contains eosinophils

The symptoms begin with the onset of warm sunny weather in the spring and persist through the summer Heat and bright light tend to aggravate the condition The itching redness and discharge usually subside at the onset of fall but in some children may last well into the winter The papular appearance of the conjunctivae is usually present in some degree throughout the year As previously noted the majority of cases tend to subside at the time of puberty

Vernal conjunctivitis is distinguished from simple allergic conjunctivitis by the characteristic papular appearance of the lesions and by the tenacious nature of the exudate Differentiation from trachoma depends on the itching the eosinophilia of the exudate and the absence of pannus

Etiologic Diagnosis

As previously indicated a large proportion of children with vernal conjunctivitis have the tendency to atopy 25 to 30 per cent have associated hay fever and an approximately equal number have some degree of allergic rhinitis due to nonseasonal allergens Most of these will show some reactions to intracutaneous tests with pollens or other inhalants The symptoms may become worse during the periods of exposure to the pollens which react in skin tests but are not limited to the seasons of these pollens so that proof of an etiologic relationship is difficult In general avoidance of reacting inhalants or injection *treatment with reacting pollens cannot be expected to satisfactorily* relieve the condition despite published reports of good results in isolated cases From the practical standpoint nothing is gained by considering these skin tests of diagnostic significance

Cooke has studied and treated cases on the hypothesis that vernal conjunctivitis is a manifestation of *bacterial allergy similar to hyperplastic sinusitis* The histologic picture of the two conditions is similar as is the association with atopy The absence of skin reactions to extrinsic allergens which adequately account for the symptoms is noted in both In a few cases injections of vaccines have been observed to cause a sudden exacerbation of symptoms similar to that noted in infective asthma Treatment with vaccines and other bacterial antigens has not however produced sufficient relief to warrant acceptance of this theory

While it is apparent that considerable evidence suggests that allergy is a factor in vernal catarrh the allergic approach does not provide an etiologic diagnosis of practical importance in treatment

Treatment

The treatment is primarily local Frequent cleansing with boric acid eye wash is soothing and helps to remove the thick exudate Cortisone ophthalmic *suspension and ointment are the most effective remedy Monohydrated* sodium carbonate 1 to 2 per cent in eye drops has also been widely used In severe cases beta radiation is often effective

Little effect on the vernal conjunctivitis itself is to be expected from allergic treatment Such treatment may be justified only by the coexistence of atopic diseases which are amenable to the method

PHLYCTENULAR KERATOCONJUNCTIVITIS

Phlyctenular keratoconjunctivitis is an inflammation of the eye characterized by the presence of 1 to 2 mm nodules with surrounding congestion occurring on the cornea or conjunctiva at or near the limbus The lesions usually ulcerate and heal rapidly without significant scarring This inflammation occurs chiefly in children with tuberculosis or poor nutrition

Evidence of an allergic mechanism is offered by experimental studies in which similar lesions were produced by instilling tuberculin horse serum and other antigens into the eyes of animals sensitized to these substances

Apparently tuberculosis is the predominant cause in children Woods states that almost all children with phlyctenules show strongly positive reactions to skin tests with tuberculin and most have or have been exposed to active cases of tuberculosis Other organisms may occasionally cause the same type of reaction Some reports in the literature have attributed the condition to allergy to foods or pollens but the evidence offered is not substantial

Study of the case should be directed at the detection of the underlying infection and treatment directed toward its control Skin tests with tuberculin and other bacterial antigens are helpful but allergic treatment is not necessary

OTHER ALLERGIC DISEASES OF THE EYE

The concept of allergy to extrinsic antigens to infective agents and to autoantigens of the tissues have been widely applied in the study of diseases of the interior of the eye particularly by Woods and his associates Discussion of these conditions is here limited to brief mention of the allergic aspects the differential diagnosis and treatment are outside the scope of this book

Uveitis

Inflammation of the uveal system is often associated with chronic disease elsewhere in the body such as tuberculosis syphilis brucellosis rheumatoid arthritis and Boeck s sarcoid In other cases the etiology is obscure The disease is divided into the relatively acute nongranulomatous type and the chronic granulomatous type The former is believed to reflect an allergic reaction to infection elsewhere the latter to result from actual infection in the uveal tract with an associated allergic reaction

Both types are relatively rare in children Kimura Hogan and Thygeson reported 18 cases in children 6 of which were associated with the types of infections noted above or other obvious causes Among the remaining 12 cases of obscure etiology there was a surprisingly high incidence of allergy Six were said to show an allergic diathesis and two others showed definite eosinophilia of the blood One child recovered after elimination of contact with a pet cat but a definite causative relationship was not claimed Allergy to foods and inhalants has been suggested as a cause of uveitis in adults (see reference to Pothman) but the evidence in many cases is open to question

Sympathetic Ophthalmia

The danger that injury to one eye may be followed by sympathetic inflammation of the other eye is well known This reaction most often follows several weeks after penetrating wounds involving the uveal tract The injury and ensuing inflammation in the injured eye are believed to permit the passage of uveal pigment through the circulation to organs of antibody formation where it acts as an antigen and causes autosensitization This in turn causes an allergic reaction with the uveal pigment of the previously sound eye manifested by a characteristic type of inflammation The development of autosensitization is explained by the fact that uveal pigment is an organ specific rather than species-specific antigen and during health does not come into contact with organs of antibody formation

Support for this view is offered by skin tests with uveal pigment Patients with active sympathetic ophthalmia consistently show after 24 to 48 hours a delayed inflammatory reaction similar in gross appearance to the tuberculin reaction Histologically the site of the skin test shows features characteristic of the eye lesion of sympathetic ophthalmia

Endophthalmitis Phacoanaphylactica

Inflammation of the eye may also follow injuries to the lenses and incomplete removal during operations for cataract This condition has been attributed to autosensitization to lens protein which like uveal pigment is antigenic and organ specific rather than species specific Skin tests with lens protein may show positive reactions in these cases but the results are less consistent than in sympathetic ophthalmia

Cataract Associated With Atopic Dermatitis

A number of authors have reported cases of cataract in young adults who had various forms of eczema particularly atopic dermatitis over a period of years While the condition occurs in early adult life it should be of interest to pediatricians who treat atopic dermatitis In most cases it has followed severe eczema which was present throughout childhood The mechanism of its development is unknown but the rarity of cataract in this age group lends credence to the view that the cataract formation is due to the allergy causing the dermatitis While the occurrence is certainly rare it gives added reason to continue actively the treatment of persistent atopic dermatitis despite occasional discouraging results

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Chapter 17

ALLERGY OF THE CENTRAL NERVOUS SYSTEM

A considerable volume of medical literature has been devoted to the manifestations of allergy in the central nervous system. This material leaves little doubt that such conditions exist but the frequency with which they occur and the actual importance of allergic sensitization in the causation of neurologic disease are subject to wide divergencies of opinion.

Evidence from animal experiments indicates that the central nervous system may be the site of at least two types of sensitization reactions: the Arthus reaction and autosensitization. Lesions of the Arthus type can be produced in the brain by the intracerebral injection of specific antigen in anaphylactically sensitized animals. Since the tissues of the central nervous system are organ specific rather than species specific, experimental production of sensitization to them is readily achieved. The occurrence of such artificial sensitization to central nervous system tissue results in the development of disseminated lesions of the brain and spinal cord characterized primarily by degeneration of myelin.

This experimental encephalomyelitis strongly resembles the clinical encephalomyelitis which occasionally follows prophylactic injections of rabies vaccine. Since this vaccine is prepared from rabbit central nervous system tissue, it appears probable that the mechanisms of the two conditions are similar. With less substantial evidence but support from the histologic nature of the lesions, spontaneous autosensitization to nerve tissue has been hypothesized as an explanation of multiple sclerosis.

An obvious but relatively rare example of clinical allergy of the central nervous system in children is the allergic meningitis which may follow intrathecal injections of antiserum and occasionally antibiotics

The principal interest however is in the application of allergic methods of diagnosis and treatment to the periodic reversible diseases of the central nervous system—headache syncope and convulsive disorders There are reports of a number of cases both in children and adults in which these manifestations have been adequately proved to result from sensitization to a specific allergen Since these diseases are usually of obscure etiology and the outlook for recovery poor the possibility of establishing an allergic cause offers an attractive hope of relief The practical question is How often is this hope justified by the results of allergic study and treatment? The answer in the opinion of the present authors is very rarely However success in one case of these discouraging diseases outweighs scores of failures so that a trial of allergic methods is warranted in cases which are not adequately handled by other methods

HEADACHE — MIGRAINE

Headache is a fairly common symptom in children old enough to describe their sensations adequately It may result from a wide variety of organic causes from fatigue or eyestrain or from emotional upsets but the actual cause is obscure in a large proportion of cases A number of the periodic headaches of obscure cause in children of 6 to 8 years or older have the typical features of migraine a severe periodic headache usually unilateral of throbbing nature preceded by an aura of visual auditory or other sensory disturbances and accompanied by nausea and vomiting Recognition of the typical case is easy but a large proportion of the cases seen in children fail to show all of these features and the separation of migraine from other periodic headaches is based on arbitrary standards which are different in various clinics Actually the attempt to set up rigid criteria for the diagnosis of migraine is not essential to a discussion of the allergic aspects since allergy has been suspected as a factor both in typical migraine and also in other periodic headaches

Typical migraine shows a distinct familial incidence which is believed to have a genetic basis The relationship of migraine to the hereditary tendency to atopic disease has been variously interpreted by different writers Statistical evaluation is made difficult by the variable criteria used in the diagnosis of migraine and the results of a number of published surveys have been distorted by including a family history of migraine as evidence of the atopic tendency Schwartz using a more objective method found no evidence of a genetic relationship between migraine and asthma which he selected as a typical atopic disease (See Chapter 7)

A number of the earlier writers on allergic diseases have set forth the opinion that migraine is a manifestation of the atopic group of diseases and some still adhere to this view On the other hand many of the outstanding authorities on allergic disease have never accepted this view nor have many

of the workers from the fields of neurology and internal medicine who have written on migraine It is the opinion of the present authors that a few isolated cases of periodic headache with some of the characteristic features of *migraine have been definitely shown to result from allergy but that the proportion* of such cases among all cases of periodic headache in children is exceedingly small

The differential diagnosis of periodic headache need not be discussed here Suffice to say that the application of the necessarily prolonged and tedious methods of allergic study which offer the prospect of satisfactory results in only a small proportion of cases should be reserved for children who have already had careful studies to exclude organic causes eyestrain and other common factors

The allergens suspected as causes of periodic headache in children are most often foods Chocolate has been incriminated particularly often The next most frequent factors are the basic foods milk wheat and eggs Occasional cases have been attributed to a wide variety of meats fruits and vegetables Headaches due to inhaled allergens is usually associated with severe allergic rhinitis and probably results from the nasal congestion Because of this apparent extracranial mechanism this type of headache is not included in the present discussion

Skin tests are not a reliable means of assessing the role of foods in causing headache Of those showing positive reactions in intracutaneous tests only a few can be shown by actual trial to be causative factors and dietary trials may show other foods which give no reaction on skin testing to be important However the tests are often useful in quickly supplying clues which could only be obtained over a period of several weeks by dietary methods

After the completion of skin tests the child is placed on a diet eliminating milk eggs wheat chocolate and any other foods which have shown moderate or marked reactions in skin tests At the same time a food diary (see Chapter 9) is started so that other possible allergenic foods may be detected Except in conjunction with the elimination diet little may be expected of the food diary method since most of the usually suspected foods are those eaten daily by a child on an unrestricted normal diet

If the elimination diet produces relief for a period of three or four times the usual interval between attacks for the particular child one may assume that a causative factor has been eliminated and proceed to restore the eliminated foods one at a time observing the effects If the first trial diet does not produce relief an attempt is made to deduce other possible allergens from the food diary and add these to the list to be avoided If clues are lacking from this source an arbitrary change eliminating other foods is made

It is apparent that the time required for obtaining results by this method depends directly on the intervals at which the child ordinarily has attacks Changes of diet made too often lead only to confusion At best the completion of the study requires many weeks

It is important to remember that the foods and symptoms recorded are the observations and reports of the child and parents and may be colored by their desires and prejudices The unreported eating of a chocolate bar at school may vitiate the interpretation of weeks of study On the other hand Wolff has pointed out that the firm belief of a group of physicians that eating chocolate invariably caused them personally to have headaches failed to be substantiated when chocolate was fed to them in a disguised form It is apparent that the simple and logical method of elimination diets may prove unexpectedly difficult in practical application

While a prolonged period of relief following the elimination of a food is a gratifying clinical result actual scientific proof of the causative relationship requires not only the absence of symptoms when the food is avoided but *also repeated demonstrations that the headache can regularly be induced* at will by adding the food to the diet Such rigorous proof may be considered unnecessary in practice but should be required of physicians who report their findings in the medical literature

When a food allergen is shown to be the specific cause of periodic headaches the logical treatment is avoidance for an indefinite period of time Desensitization is rarely possible The symptomatic treatment of the attack with ergotamine caffeine aspirin and sedatives is outside the scope of this book Antihistamines are not effective except as mild sedatives

EPILEPSY

The problem of the relationship of allergy to epilepsy and related convulsive disorders is quite similar to that in regard to migraine A number of *cases of convulsive disorders in children fairly clearly shown to be related to* specific food allergens have been reported in the literature By the available methods of study these conditions were otherwise indistinguishable from epilepsy On the contrary application of allergic methods to the study of large unselected groups of epileptic children has not produced a significant number of good results Bridge reported that not one of a series of 742 convulsive disorders in children could be related to a specific food allergen Other workers have felt that allergic methods were helpful in the treatment of children with epilepsy and coexisting allergic disease although the concurrent use of anticonvulsive drugs was usually necessary

Evidence that the atopic diseases may affect the cerebral cortex is offered by studies of the electroencephalogram Such tracings have shown an incidence of abnormal patterns in 33 to 50 per cent of allergic children as compared to 5 per cent in normal nonallergic children These abnormal patterns do not signify the presence of clinical convulsive disorders as the 33 per cent incidence applied to a group of asthmatic children from which all those with a personal or family history of convulsive disease were carefully excluded The significance of these findings is not apparent

Some of the cases of allergic convulsive disorders of children have been associated with urticaria due to the same cause Other cases described have

been associated with other atopic diseases not caused by the same allergen. The coexistence of atopic disease in a child with epilepsy apparently increases the possibility that the convulsions may be on this basis but is of course not proof of the relationship.

In the cases of convulsive disorders of children believed to be due to allergy the allergens most ofen involved were the common foods milk wheat eggs and chocolate.

The results of intracutaneous tests with the foods in such cases are variable and do not form a basis for diagnosis. In general the diagnosis is established by the use of diets eliminating the four foods just mentioned with a food diary kept simultaneously in an attempt to relate any attacks which occur to other foods eaten. No significant results can be expected if the diet is given while the disease is well controlled with anticonvulsive drugs. On the other hand if the symptoms are well controlled by drugs the small chance of success of the allergic method may make one reluctant to withhold the drugs for the required period of time.

The situation may be summarized by the statement that very few cases of the convulsive disorders of children can be shown to be due to allergy the coexistence of obvious atopic disease with the convulsive disorder suggests a slightly greater possibility of success but trial of the allergic method is warranted because of the poor outlook for relief by any other method.

BEHAVIOR DISORDERS

Concurrently with the extensive psychiatric literature linking allergic diseases with emotional and psychic causes there has been a smaller volume of papers attributing emotional and behavior disorders of children to specific allergic causes. Several authors have described cases in which dramatic improvement in the character and behavior of unmanageable children has followed elimination of certain foods or other measures directed at specific allergens.

It is well known that serious chronic allergic disease may affect a child's emotional adjustment. Frequent attacks of asthma may prove essentially as disabling and as disturbing to relations with other children as epilepsy. Both the persistent itching and the disfigurement of atopic dermatitis may cause a child to become nervous shy and irritable. In such cases improvement of the physical state may be expected to improve the child's social adjustment.

It is more difficult to evaluate reports in which severe disturbances of emotions and behavior with minor or no physical manifestations of allergy have been attributed to sensitization. In most cases an allergic cause has been suspected on the basis of a past history of allergic disease or a strong family history. The specific allergens have in most cases given positive reactions on skin test and elimination has been followed by improvement in the behavior and social adjustment. In few instances has an attempt been made to reproduce the symptoms by intentional exposure to the suspected allergen. It is possible that in some instances the personality disorder may have been due to specific allergy. However it should not be anticipated that the correction of minor allergic symptoms or the avoidance of allergens which are not causing

physical evidences of allergic disease will lead to a change of personality or behavior in any appreciable number of maladjusted children Just as the allergic approach is the most fruitful in asthma the psychiatric method offers the greatest prospect of success in true behavior disorders

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Chapter 18

CONTACT DERMATITIS

TERMINOLOGY

As the outer layer of the body affording protection to the other organs the skin is naturally exposed to a variety of irritating and injurious materials The inflammation of the superficial layers of the skin which results from the effects of the contact of injurious substances with its surface is designated as *contact dermatitis* Certain substances such as strong acids and lye which by their chemical nature are naturally irritating to the skin are designated as *primary irritants* Other substances classed as *sensitizing agents* are not injurious to normal skin on the first contact but penetrate into it and set up an allergic sensitization so that subsequent contact of the skin surface with the same substance causes inflammation It is the latter or allergic type of contact dermatitis that chiefly concerns us here This is typified by poison ivy or *Rhus toxicodendron* dermatitis While Rhus dermatitis has been shown to depend on acquired sensitization rather than primary irritation the allergy is so frequent among persons exposed to the plant that it is commonly thought of as toxic This idea is expressed in the terms poison ivy and *dermatitis venenata* often used to designate the disease

Some confusion may result from the differences in the terminology employed in Europe and America In Europe contact dermatitis is often called eczema or eczematous dermatitis while in America the word eczema is chiefly used in the term infantile eczema to denote the infantile form of atopic dermatitis a distinctly different type of allergic skin disease The word eczema used alone is descriptive of a general type of dermatitis rather than an exact diagnostic term

ETIOLOGY

Differentiation between primary irritants and sensitizing agents is a basic point in the etiology of contact dermatitis. The distinction is not always easy since some chemically active agents may act as primary irritants when applied to the skin in a relatively high concentration and as sensitizers when present in a diluted form. In general, primary irritants are chemically very active compounds and are encountered less often as natural substances than as manufactured products. On the other hand, extremely active sensitizers such as poison ivy occur in nature. Some of these affect such a large proportion of exposed persons that proof of the concept that the dermatitis depends on the development of acquired sensitization rather than primary toxicity is not simple. Following the demonstration by Jadassohn that contact dermatitis due to the primrose (Primula) was an acquired allergy, Spain, Strauss and others showed that poison ivy had no toxic effect on the skin of persons who had not been previously exposed to it, notably infants and Eskimos. When the tests were repeated on the same individuals two or more weeks later, a considerable number developed dermatitis, indicating that they had been sensitized by the first contact.

With active sensitizing agents such as poison ivy, 70 to 80 per cent of people become allergic after repeated contact. Experimental studies with some of the chlorobenzene compounds indicate that essentially all persons will acquire this type of sensitization if adequately exposed to a sufficiently active sensitizing agent. There are considerable differences in individual susceptibility; whether these variations depend on skin texture or immunologic reactivity is not clear. Clinically there is no evidence that heredity is an important factor, and susceptibility to contact dermatitis is not related to the atopic tendency. In careful breeding experiments with guinea pigs, Chase has shown that susceptibility to contact dermatitis is influenced by heredity, but the genetic mechanism involves several different factors and is too complex for analysis by Mendelian principles. If such a mechanism exists in the human species, it could scarcely be detected because of unselected matings, so that in practice heredity is not an apparent factor in clinical contact dermatitis.

While contact sensitization typically results from absorption of allergen through the normal, unbroken skin, its development is facilitated by scratches, burns and other inflammations of the exposed skin area. Children whose skin is already affected by allergic disease of the atopic or contact types are particularly apt to become sensitized to new contact allergens, notably to topical medications.

The substances causing contact dermatitis are of such solubility and diffusibility that they can pass through the unbroken skin surface. In general, proteins do not have this property, and they are not a significant factor in the etiology of this form of sensitization. On the other hand, many organic compounds of the aromatic group, both natural and synthetic, metallic salts and other substances of relatively low molecular weight are important causes.

Most of the important causative agents are not typical antigens in that they do not cause the formation of precipitating antibodies when injected into experi

mental animals in their uncombined form. There is considerable evidence that they act as *haptens*, combining with the body proteins and altering their specificity so that the hapten-protein complexes react as foreign antigens. The exact mechanism of combination with protein is not known in every case, but Landsteiner has shown in studies of the halogenated benzene compounds that sensitizing activity is proportional to chemical reactivity in combining with proteins.

In childhood the most important etiologic factors are lipoid and resinous substances derived from plants, chiefly those of the genus Rhus, which includes poison ivy (*Rhus toxicodendron*), poison oak (*R. diversiloba* and *R. quercifolium*), and poison sumac, of which there are several closely related species. The exact botanical classification appears to be open to question, and several of these plants may be varieties of the same species. Japanese lacquer is derived from an Asiatic species of Rhus. When thoroughly dried, the lacquer is relatively innocuous but may still occasionally cause dermatitis. The species of Rhus may grow as vines, shrubs, or small trees. The poison ivy and oak have typical leaves composed of three leaflets, but the leaves of sumac may have 7 to 13 leaflets. The principal allergen, urushiol, a catechol with an unsaturated side chain and the formula $C_6H_3(OH)_2C_{15}H_{27}$, is apparently common to the various species. It is inactivated by oxidation and precipitated in an inert form by metallic salts of iron, lead, and zirconium. It is soluble in ether, acetone, and oils, but not in water. However, it may be effectively removed from the skin by scrubbing with soap and water. It is not volatile at ordinary temperatures, but may be carried by particles in the smoke when the plants are burned. The allergen occurs in the sap of the plant, and the leaves and stems are most dangerous during the spring and summer.

The flowering primrose (Primula), which is more common in Europe than America, contains an allergen which is essentially as active as that of poison ivy and is a frequent cause of contact dermatitis in children who are exposed to it. Many other plants contain substances which are less active sensitizers but may occasionally cause dermatitis. Among these are the leaves and stems of garden vegetables such as the carrot, tomato, and potato, flowering plants such as the tulip, dahlia, and chrysanthemum, and the peel of the orange and other citrus fruits. The active materials are lipids which may be extracted with ether and used for diagnostic patch tests. Many weeds contain similar allergens in their stems, leaves, and pollen. Ragweed pollen may cause contact dermatitis, but usually only after relatively heavy exposure such as direct contact with the pollenating plant. In this instance also, the contact allergen is a lipoid substance distinct from the proteins which act as antigens in hay fever. Pyrethrum, a flowering plant which is widely used in insecticide powders and sprays, is important as a household contact which may cause contact dermatitis.

Of the textile fibers, silk and wool are possible causes of contact dermatitis, the irritation produced by wool resulting from mechanical irritation as well as sensitization. Dyes and finishes used on these and other fabrics are

also possible causes of allergic reaction If a child is highly susceptible to contact dermatitis it may be wise to wash new clothes if possible before they are worn

The typical diaper rash affecting the buttocks of infants allowed to lie in wet diapers is most often due to the presence in the diapers of saprophytic bacteria which split urea in the voided urine to produce ammonia in concentrations acting as a primary irritant to the skin In such cases the ammoniacal odor of the wet diapers is usually very apparent The condition is benefited not only by more frequent changing of the diaper but also by boiling the diapers in the process of laundry to kill the bacteria This may also be accomplished by soaking the diapers in antiseptic solutions but the various mercury compounds most often used for this purpose in commercial laundries occasionally act as sensitizing agents

Rubber and plastic are common causes of contact dermatitis and may affect infants about the buttocks where rubber or plastic pants touch the skin or elsewhere from contact with rubber sheeting Soaps and detergents used for laundry are possible factors and metals particularly nickel are occasional causes of contact sensitization in children

A wide variety of topical medications may cause sensitization Among the most common offenders are mercury compounds sulfonamides penicillin local anesthetics and antihistamine drugs When ointments containing these drugs are used for more than a few days one must be alert to the possible development of an allergic reaction

IMMUNOLOGY AND PATHOLOGY

The contact type of sensitization is induced most readily by application of the causative agent to the skin surface such superficial contact being more effective than experimental subcutaneous intramuscular or intraperitoneal injection With active sensitizing agents the development of allergy may become apparent within a week or two after the first contact If several areas of the skin have been successively exposed to the same agent the development of sensitization may be followed by flare ups of dermatitis at the previously exposed sites the concentration being greatest in the sites most recently exposed *The skin sensitization resulting from a single exposure is general* but may be somewhat more acute in the area of actual contact

After sensitization has occurred subsequent contact of the specific allergen with the skin causes a delayed type of reaction appearing 24 hours or more after exposure This reaction consists primarily of edema of the epidermis (spongiosus) with vesicle formation It does not have the typical features of a histamine reaction and is not influenced by antihistamine drugs When the sensitized individual is exposed to the allergen in the natural manner by surface contact the reaction is essentially limited to the skin In most cases the mucous membranes show little if any reaction to the allergen apparently due to washing away of the allergen by the secretions There is evidence that other organs are also sensitized If a person who has had contact derma

titis due to one of the sulfonamide drugs subsequently takes the same drug by mouth a systemic reaction with fever malaise and intense eosinophilia may occur in addition to development of a generalized skin rash The presence of visceral sensitization is also manifested in several reports of serious kidney damage following the injudicious injection of Rhus allergen into patients with acute dermatitis due to this plant

In contact sensitization no specific antibody can be demonstrated in the plasma or serum However as previously noted Chase has shown that contact sensitization of guinea pigs may be passively transferred to normal pigs by injection of lymphoid cells of the spleen pulp and monocytic peritoneal exudates apparently indicating the presence of a cellular type of antibody which carries the sensitization The transfer of the allergic reaction by these mesenchymal cells is in itself evidence that sensitization is not limited to the skin (See Chapter 2)

DIAGNOSIS

Symptoms—The characteristic lesion of contact dermatitis is the vesicle These may vary from pin point size to large blebs 1 or 2 cm in diameter They usually occur in clusters on an erythematous base The superficial layers of the skin are edematous in the affected areas and when the eyelids ears or genitalia are involved there may be marked subcutaneous edema The vesicles are easily broken down by scratching with the development of an oozing surface Subjectively there is intense itching of the affected areas but usually no significant general symptoms

Any area of the skin may be involved but the palms soles and scalp are relatively resistant The initial distribution of the lesions corresponds to the skin area exposed to the allergen but in dermatitis due to very active allergens they may subsequently be spread by scratching

The lesions characteristically make their appearance one or two days after exposure to the allergen but the interval may be longer or shorter depending on the degree of sensitization

Differential Diagnosis—The recognition of contact dermatitis depends on the occurrence of an itching vesicular rash in a distribution consistent with the area of contact with a potential causative agent The distribution obviously depends on the causative agent Poison ivy dermatitis usually appears first on the dorsal surface of the hands and feet in the interdigital spaces on the legs arms and face but may be spread to other areas by scratching The lesions often have a linear distribution which may follow scratches received from briars or other vegetation Dermatitis due to household contacts also tends to affect primarily the exposed areas of the skin Rashes due to articles of clothing naturally affect the covered areas of the body

In the differentiation from atopic dermatitis the vesicular character of the early lesions is helpful but the characteristic appearance may be destroyed by scratching A predilection for the face neck and antecubital and popliteal spaces is suggestive of atopic dermatitis but any of these areas may be affected

by contact dermatitis The personal or family history of atopic disease and an atopic tendency manifested by immediate wheal reactions to skin tests obviously suggest *atopic dermatitis but contact dermatitis is so common in* all children that the presence of atopy in no way excludes it

Other types of dermatitis from which contact dermatitis must be distinguished include seborrheic dermatitis infectious eczematoid dermatitis fungus infections and intertrigo Seborrheic dermatitis affects primarily the scalp which is usually relatively resistant to contact dermatitis but may also involve the skin folds about the nose and ears The lesion is characteristically scaly usually greasy without vesicles Infectious eczematoid dermatitis usually affects areas of skin exposed to the infected discharges of the ears nose etc Fungus infections of the scalp and circinate lesions of the body present a fairly characteristic appearance differing from the usual features of contact dermatitis Ringworm of the feet most often affects the interdigital spaces but lesions may occur on the sides of the feet and resemble areas of contact *dermatitis due to materials in the shoes In doubtful cases smears and cultures* for the fungus may be helpful Tinea cruris and intertrigo characteristically occur in skin folds where contact dermatitis is less common When only a few closely grouped vesicle are present at the onset differentiation from insect bites may be difficult but if the condition progresses to a significant degree the diagnosis is usually apparent

Specific Diagnosis—Diagnosis of the specific causative factor is based on deduction from the distribution of the rash the known contacts and the history of previous attacks The suspicion may usually be confirmed by the patch test if necessary *If a child is known to be allergic to poison ivy and develops* a rash on the legs after a picnic in a location infested with the plant no patch test is needed On the other hand if one suspects an eruption is due to tomato vines or dahlias it is useful as proof

The ***patch test*** consists essentially of an attempt to reproduce the dermatitis by the application of the suspected cause to a localized area of uninvolved skin under controlled conditions Since the skin allergy is usually general the percentage of success is high if the conditions are properly chosen However dermatitis limited to the most delicate areas of skin such as the eyelids may not be elicited when the same agent is applied to *the thicker and tougher skin of* the back or extremities which are the most convenient and frequently used sites for testing To some extent this difficulty is overcome by using a more prolonged and intense exposure during the test In order to obtain significant results *it is essential that the suspected allergen be applied in a concentration* which does not irritate normal skin Suitable concentrations of some of the more common agents are shown in Table XVII Some of these are from Sulzberger s *Office Immunology* which gives a far more complete list When using materials for which no specific concentration is recommended control tests on presumably normal persons are helpful

The material is generally applied to a piece of gauze about 1 cm square covered with a slightly larger square of cellophane or waxed paper and the whole then covered with adhesive tape Since adhesive tape itself may cause

skin irritation it is advisable that a margin of cellophane or other inert material extend between the suspected substance and the adhesive One may conveniently employ small prepared 3 to 4 cm square adhesive dressings applying the test material to the center of the gauze pad Dry materials should be moistened with saline The tests are placed on clean normal skin of the arm thigh or back If difficulty is encountered in keeping them in place for the desired period of time the area may be bandaged or covered by a larger protective dressing

The period of contact is usually two or three days but if severe itching suggests that an excessive reaction is occurring on the first or second day the patch is removed promptly and the material washed off with soap and water or suitable solvents Positive reactions are usually apparent as localized areas of dermatitis when the patches are removed but occasionally become evident only a day or two after removal

TABLE XVII

SUITABLE CONCENTRATIONS OF ALLERGENS FOR PATCH TESTING

Ammonium fluoride 2% aqueous solution
Anesthesin ointment 5%
Benadryl ointment as is
Cloth as is
Copper sulfate 5% aqueous solution
DDT 5% in acetone
Leather as is
Linseed oil as is
Mercuric chloride 0.1% aqueous solution
Nickel sulfate 5% aqueous solution
Orange peel as is
Paraphenylenediamine 2% in Vaseline
Plant leaves (except Rhus) as is
Plastic as is
Poison ivy 1% in alcohol
Procaine 1% aqueous solution
Pyrethrum (powdered) as is
Pyribenzamine ointment as is
Rubber as is
Soap 5% aqueous solution
Surfacaine ointment as is
Thephorin ointment as is
Turpentine 25% in vegetable oil

In part from Sulzberger M B Office Immunology Chicago 1947 The Year Book Publishers Inc

PROPHYLAXIS AND TREATMENT

Prevention —When the causative agent of contact dermatitis has been determined the obvious treatment is avoidance to exposure This usually presents no serious problem except in the case of poison ivy and related species of Rhus In so far as practical poison ivy should be destroyed in yards and play areas by carefully pulling the vines in the winter or early spring and spraying any remaining plants repeatedly during the summer with 2 4D or other herbicides Since the allergy is readily acquired by most children on

repeated contact and persists indefinitely it is best that children (and parents) be taught to consider these plants as a potential danger to everyone regardless of whether or not the individual has previously shown evidence of sensitization Children old enough to play outdoors unattended should be taught to recognize and avoid the species of Rhus growing in their locality

In the case of highly susceptible children indirect contact with poison ivy may produce dermatitis The danger of exposure to the smoke of burning the plants is well known Less recognized is the risk of acquiring dermatitis by contact with dogs and cats which have run through the vines To a less extent clothing toys and balls may carry the irritating material

When contact with poison ivy or other contact allergens is unavoidable a measure of protection may be gained by applying protective creams containing silicones to the exposed skin areas before exposure These form a relatively impervious coating which prevents penetration of irritants into the skin but is easily removed by soap and water Whether or not they are used the skin should be carefully scrubbed with soap and water after actual or presumed contact with the plants Prompt washing away of the irritant material before it penetrates the skin is far more effective than any subsequent corrective treatment

Treatment —The treatment of contact dermatitis depends upon the stage extent and severity of the eruption Many cases due to household contacts and topical medication clear promptly when contact is avoided so that no other treatment is needed At the onset of poison ivy dermatitis liberal use of soap and water is still indicated to remove any traces of the allergen remaining on the skin surface Applications containing zirconium oxide which chemically inactivates the antigen are also recommended Rhulicream (1 per cent zirconium oxide with 1 per cent benzocaine) and Ziradryl (4 per cent zirconium oxide with 2 per cent Benadryl) are suitable proprietary mixtures For the relief of itching calamine lotion with phenol and similar shake lotions are helpful Antihistamine drugs have no effect on the course of the rash but are useful both locally and systemically to relieve itching This effect apparently results from their local anesthetic action rather than antihistaminic properties There is no evidence that histamine plays a significant part in the disease When antihistamine drugs are used topically one must be alert to the possibility of sensitization to the medication which may occur at the end of a week of exposure

When vesicles are well developed the same antipruritic medication may suffice if the rash is limited to small areas and shows little tendency to spread For more active treatment hydrocortisone 1 per cent or fluorohydrocortisone 0 25 per cent ointment is useful When the vesicles have broken down to form oozing or crusted areas wet dressings with potassium permanganate 1 5 000 or aluminum acetate are indicated This may be followed by one of the hydrocortisone ointments after one or two days when the oozing ceases

In cases of extensive or rapidly spreading dermatitis especially if the face is severely affected the systemic use of cortisone prednisone or corticotropin may be advisable With adequate doses of these drugs the symptoms may usually

be controlled within two or three days Gradually decreasing doses may then be continued for seven to ten days until the rash has cleared If further contact with the allergen has been avoided recurrence after stopping the drug is not common When it does occur it will usually yield to local use of hydrocortisone

Injections of the allergen of poison ivy should not be used in treatment of the active eruption as they often cause severe exacerbations and occasionally systemic reactions

Immunization —Children who are highly susceptible to the Rhus allergen and who continue to have frequent attacks despite all possible measures to avoid contact should be immunized during a free interval preferably early in the spring Several controlled studies offer ample evidence that tolerance may be considerably improved by this procedure but complete immunity is not to be expected and care to avoid contact must be continued Many different preparations of the allergen and programs of treatment have been advised For oral immunization tincture of *Rhus toxicodendron* may be diluted a hundredfold in syrup of orange with 2 per cent alcohol added The first dose is 1 drop and is increased by 1 drop after each meal to 20 drops then 1 teaspoonful daily through the period of exposure All doses are given in at least a half glass of water No serious toxic effects are expected but dermatitis about the anus occasionally develops as a result of the passage of allergen in the stools

Injection treatment insures more complete absorption of antigen than oral administration and does not necessitate daily dosage during the season The most generally used antigen for injection is a solution of antigen in vegetable oil (usually corn or peanut oil) The allergen is relatively stable in this preparation and the extract is essentially painless when injected intramuscularly or deeply subcutaneously Extracts in absolute alcohol were formerly widely used but are unstable and must be diluted with about 20 volumes of saline diluting fluid immediately before use to lessen the pain of injection

Treatment should not be started during the acute attack and preferably 6 to 8 weeks before the anticipated time of exposure The dosage must be adjusted according to the degree of sensitization but need not be individualized to so great a degree as treatment with pollen extracts An initial dose of 0 1 ml of 0 01 per cent extract in oil is safe for practically all children The subsequent doses are given at intervals of five to seven days and increased as indicated in Table XVIII Extremely sensitive patients may be unable to tolerate injections larger than 0 5 ml of 0 1 per cent extract larger doses producing excessive local reactions and small patches of dermatitis after each injection When this occurs no further increase should be attempted but the highest dose which is well tolerated repeated every 2 to 4 weeks through the season Most patients are able to follow the schedule up to 0 3 ml of 5 per cent extract This dose is then continued every 2 to 4 weeks during the season of exposure

Spain and Strauss have recommended the use of a pyridine extract of the allergen precipitated with alum and resuspended in an aqueous medium This particular antigen is believed to be more slowly absorbed than the oily

solution lessening the chance of an excessive reaction to the injection and enhancing the immune response This preparation is injected subcutaneously at intervals of 7 to 10 days until a full dose is reached (Table XVIII) then repeated every 2 to 4 weeks through the season Reported results indicate that this material may be fully as effective as the oily extract but so far it is backed by less extensive clinical experience

The protection conferred by injection treatment is only partial and does *not eliminate the need for avoiding excessive exposure to the plant* However in those cases where all reasonable attempts to keep the child from contact have failed to prevent recurrences the results of treatment are usually

TABLE XVIII

DOSAGE OF POISON IVY ALLERGEN FOR PROPHYLACTIC TREATMENT

DOSE	OIL EXTRACT		ALUM PPT	PYRIDINE EXTRACT
1	0.01%	0.1 ml	1:50	0.1 ml
2	0.01%	0.3 ml	1:50	0.2 ml
3	0.01%	0.5 ml	1:50	0.3 ml
4	0.1%	0.1 ml	1:50	0.5 ml
5	0.1%	0.3 ml	1:50	0.7 ml
6	0.1%	0.5 ml	1:5	0.1 ml
7	1%	0.1 ml	1:5	0.2 ml
8	1%	0.3 ml	1:5	0.3 ml
9	1%	0.5 ml	1:5	0.5 ml
10	5%	0.2 ml		
11	5%	0.3 ml		

Highest tolerated dose repeated every 2 to 4 weeks during season

very satisfactory The tolerance produced does not persist and the treatment must be repeated each year Perennial treatment with monthly injections during the winter has been employed with both the oily and alum precipitated extracts but evidence of its superiority over the preseasonal treatment has not been established

PROGNOSIS AND COMPLICATIONS

The acute attack of contact dermatitis rarely lasts more than two weeks after exposure to the allergen is terminated In most cases the skin is left without blemishes Sensitization apparently persists indefinitely and recurrence is to be expected from repeated contact with the causative agent

As in any itching eruption scratching may lead to secondary infection This may require local or general use of antibiotics in conjunction with the antiallergic treatment Ointments containing *neomycin or Terramycin in combination* with hydrocortisone are useful in such cases

While there is evidence that visceral as well as skin sensitization occurs in severe contact dermatitis systemic symptoms rarely result from natural exposure to contact allergens On the other hand severe kidney damage has been reported after the injection of Rhus allergen in the course of acute contact derma

titis Since there is little or no evidence of therapeutic benefit to offset this serious risk the use of Rhus antigen for treatment of active dermatitis is not advised

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Chapter 19

DELAYED ALLERGY TO INFECTIVE AGENTS

[illegible] the phenomena first included in the concept of allergy were [illegible] to infective agents, notably the tubercle bacillus and vaccinia virus, [illegible] from previous infection by these agents. In the subsequent study of [illegible] concentration on the [illegible] and other immediate [illegible] the attention devoted to reactions of this type. However, [illegible] infective agents has shown allergy to be a [illegible] in many infections. From the [illegible] has been the development of skin [illegible] diseases.

TYPES OF ALLERGIC REACTIONS TO INFECTION

[illegible] For example, during [illegible] pneumonia [illegible] During [illegible] These reactions [illegible]

[illegible]

that these lesions are allergic is offered both by pathologic studies of their similarity to lesions of spontaneous and experimental serum allergy and clinical studies of the association of rheumatic fever with hemolytic streptococcus Specific skin test reactions cannot be demonstrated and the role of allergy is of theoretical rather than immediate practical importance

Evidence that some cases of diseases of the *atopic* type may result from a different kind of allergic reaction to bacteria has been discussed in Chapter 7

The fourth and most widespread type of allergy to infective organisms is the delayed reaction typified by the tuberculin test It is with this type of sensitization that this chapter is primarily concerned

ORGANISMS INDUCING DELAYED ALLERGY

The number and variety of infective agents which have been shown to produce the delayed type of sensitization are so great that it appears probable that the phenomenon occurs to some degree in essentially all infections Its importance as a factor influencing the pathogenesis of disease is greatest in the chronic infections and it is in this group that diagnostic skin tests based on the delayed allergy are most often of value

Among the bacterial diseases tuberculosis is the classic example the study of which has been the basis of much of the knowledge of this type of sensitization Well marked sensitization of this type is apparent in most cases of brucellosis glanders and tularemia Less striking but definite evidence of this type of reaction is observed in typhoid fever chancroid and whooping cough The development of similar sensitization occurs during acute infections with staphylococci streptococcus and pneumococcus In these infections its importance both pathologically and diagnostically is limited by their acute course although there is evidence that it plays a significant role in recurrent erysipelas

In the systemic fungus infections development of a high degree of allergy to the infective organism is the rule and its importance both in influencing the course of the disease and for diagnostic skin tests is similar to that in tuberculosis In localized fungus infections of the skin and mucosa such as epidermatophytosis much of the tissue reaction at the site of the infection depends upon acquisition of the delayed type of sensitization and in some cases allergic phenomena (dermatophytids) may be apparent in portions of the skin remote from the organism

Among the virus diseases the classic example of vaccinia virus has already been mentioned The sensitization is most important in the more prolonged virus diseases such as lymphopathia venereum and cat scratch fever In mumps it is of sufficient degree to furnish a skin test of some diagnostic value and suggestive evidence of sensitization has been reported in herpes simplex measles and influenza

In syphilis sensitization to the spirochete undoubtedly plays a part in the changing character of pathologic manifestations from the primary to the tertiary stage and can be demonstrated by the luetin test However the diagnostic importance of this reaction is overshadowed by the availability of greatly superior serologic methods

In the case of infestation by metazoan parasites the sensitization induced is primarily of the immediate type but the delayed type of reaction is also frequently observed Thus the Casoni skin test in echinococcus disease may elicit both immediate and delayed responses

NATURE OF THE DELAYED REACTIONS

The principal immunologic features of the delayed type of bacterial sensitization have been presented in Chapter 2 Clinically the skin reaction is an *inflammatory reaction with redness and induration appearing after about twenty four hours* in contrast to the immediate urticarial reaction seen in atopy and anaphylaxis The delayed reaction lasts several days and in some cases may progress to necrosis and scarring

As in atopic disease injection of too large a dose of antigen for the skin test may produce a general reaction but the nature of the constitutional reaction is also different It is also delayed several hours after the injection and characterized by fever and malaise rather than symptoms of the anaphylactic type There are no special shock organs as in the anaphylactic or atopic reactions essentially all cells of the body seem to be affected with injury and necrosis most marked in those exposed to the greatest concentration of allergen During the general reaction lesions of the disease which harbor organisms tend to be activated presumably through double exposure to antigen locally and through the circulation

EFFECT OF BACTERIAL ALLERGY ON PATHOGENESIS OF INFECTIOUS DISEASES

In tuberculosis the effect on the host of acquiring sensitization to the infecting organisms is essentially that of converting an organism without a toxin into one whose products cause necrosis of cells exposed to them This is manifested by the change from the primary stage in which the bacteria exist in the tissues without eliciting much reaction to the fibrocaseous stage in which the presence of the organism causes death of tissue and scarring Acute exudative manifestations such as pleurisy with effusion appear to result from an intense allergic reaction to the presence of relatively few organisms A similar course of events is seen in the progression of syphilis through the primary secondary and tertiary stages as hypersensitivity to the spirochete develops The same factors appear to determine the pathogenesis of most of the fungus diseases

In other chronic diseases such as brucellosis a high degree of allergy is manifested by skin tests but the pathologic analogy is incomplete the focal *necrotic lesions failing to develop*

The few examples cited indicate the importance of bacterial allergy in determining the course and manifestations of chronic infection For greater detail the reader is referred to A R Rich s *The Pathogenesis of Tuberculosis*

RELATION OF BACTERIAL ALLERGY TO IMMUNITY

Since the development of sensitization is one aspect of the antibody response to invading microorganisms, it is apparent that the allergic reaction is closely

related to the immune processes which confer acquired resistance to infection Whether or not the actual allergic reaction to the organism is a factor in protection has proved a difficult and controversial question

The development of allergy obviously increases the ability of the organism to cause damage to the tissues adjacent to it but it has been suggested that this local damage performs a function in preventing further invasion and spread of the infective agent in the body Actually there is little direct evidence to support this view and some grounds for believing that the increased local reaction may actually lessen resistance

The complexity of the problem is increased by the fact that most pathogenic organisms contain a number of antigenic substances which induce different immunologic responses in the body In many organisms the response to one of a number of the potential antigens appears to determine the effective resistance of the host to the infective agent Whether or not the allergic reaction is to this crucial antigen can only be learned by detailed study of the particular infection The *immediate* allergic reaction to the specific capsular carbohydrate noted in convalescence from pneumococcal pneumonia appears to depend upon the development of the same antibody which protects against reinfection by pneumococci of the same type and the appearance of the positive skin test is significant evidence of the acquisition of immunity In the case of the delayed type of bacterial allergy to various organisms which have been studied the allergic reaction appears to be induced by different antigens than those stimulating protective antibody formation and therefore unrelated to acquired resistance By various procedures of antigenic stimulation passive transfer of immunity and desensitization it is possible to produce experimentally delayed sensitization without immunity or immunity without allergy The preponderance of evidence therefore suggests that this form of allergy is not protective

DESENSITIZATION

In general the delayed type of bacterial allergy may be abolished by a suitable program of desensitization with injections of gradually increasing doses of the specific antigen although the procedure is usually longer and more difficult than in anaphylactic sensitization Despite the evidence which indicates that delayed sensitization is harmful rather than protective attempts at desensitization have proved to be of little practical value in the treatment of infectious diseases and carry considerable danger of excessive general reaction For this reason the method is rarely used in clinical medicine particularly since the various antibiotic agents have been available

DIAGNOSTIC SKIN TESTS DEPENDENT ON DELAYED ALLERGY

The practical value of the delayed type of allergy to infective agents is chiefly in diagnostic skin tests for infection Such tests play an important part in the diagnosis of many infections The most serious limitation in their use is the fact that once sensitization of this type is acquired it tends to persist indefinitely regardless of the course of the illness Thus a positive skin reaction

may indicate either active disease or past infection from which there has been complete recovery. Furthermore the degree of skin reaction may vary during the course of the infection and occasionally the skin reaction is negative while the infection is obviously active. Skin tests are used chiefly in those conditions where isolation of the causative organism is difficult or impossible and reliable serologic tests are not available. In certain diseases such as brucellosis the performance of the skin test may produce enough antigenic stimulus to cause antibody formation and invalidate the results of subsequent serologic tests. In those diseases where both serologic methods and skin tests are available it is wise to exhaust the diagnostic possibilities of the serologic tests before trying the skin test reactions.

In general the tests for delayed sensitivity to infective agents are carried out by the intracutaneous method using a filtrate, vaccine or protein derived from the organism or, in the case of certain virus diseases, exudate from the lesions of known cases. For tuberculosis the Vollmer *patch test* has been developed which gives results in 90 per cent of cases comparable to the intracutaneous test (Mantoux). This avoids the needle puncture to which many children object and has the advantage for large surveys of eliminating the need of sterile syringes and needles. It is of theoretical interest in showing the fundamental similarity between the delayed bacterial reaction and contact dermatitis.

TABLE XIX

DIAGNOSTIC TESTS FOR DELAYED ALLERGY TO INFECTIVE AGENTS

TYPE OF AGENT	DISEASE	ANTIGEN	NATURE OF ANTIGEN
Bacteria	Tuberculosis	Old tuberculin	Culture filtrate modified by heat
		PPD	Purified protein from bacillus
		Vollmer patch	Dried old tuberculin
	Brucellosis	Vaccine	Heat killed organism
		Brucellin	Culture filtrate
		Brucellergen	Nucleoprotein from organism
	Tularemia	Vaccine	Formalin killed organisms
Fungus	Coccidioidomycosis	Coccidioidin	Culture filtrate
	Blastomycosis	Vaccine	Heat killed organisms
		Blastomycin	Culture filtrate
	Histoplasmosis	Histoplasmin	Culture filtrate
	Moniliasis	Oidiomycin	Culture filtrate
	Trichophytosis	Trichophytin	Culture filtrate
Virus	Mumps	Vaccine	Egg yolk sac vaccine
	Lymphopathia venereum	Frei	Heated virus from known lesion
	Cat scratch fever		Heated virus from known lesion
Metazoa	Echinococcus	Casoni	Fluid from cyst

Skin tests with filtrates of cultures of hemolytic *Staphylococcus aureus* differ somewhat from the typical reactions of delayed bacterial allergy since the materials used contain toxins as well as antigens. The reactions produced are essentially similar in appearance but the interpretation of the results depends upon the dilution of the toxic filtrate employed. With typical preparations of

high toxicity a reaction to the intracutaneous test with a 1 1000 dilution is considered evidence of allergy

Some of the skin tests for sensitization of this type which are of diagnostic value are included in Table XIX It is scarcely necessary to reiterate that these tests are for allergy resulting from present or past infection and not of susceptibility as are the Schick and Dick tests

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Chapter 20

ALLERGIC PURPURA

The diagnosis of allergic purpura is often raised for consideration but the frequency with which purpura may be ascribed to specific extrinsic allergens is relatively small. Cases of purpura due to food allergy have been described, sensitization to infective agents or their products is frequently suspected but difficult to prove, and certain cases apparently result from drug allergy.

Nature of Purpura

The term purpura denotes a condition in which there is bleeding from the small blood vessels into the skin and mucosae producing red or purple spots varying in size from pin point petechiae to ecchymoses of considerable size. The extravasation of blood may follow mild trauma or occur without apparent cause.

The retention of blood in the capillaries and other small vessels depends not only on the integrity of their walls but also on the presence of platelets or thrombocytes in the blood which tend to accumulate at sites of injuries to the walls and help to repair the defect. Purpura may result from disease of the walls of the small vessels or from lack of an adequate number of blood platelets.

The presence of purpura is usually apparent from the nature of the rash. Since the discoloration is due to blood outside the vessels it does not blanch on pressure. The resistance of the small vessels of the skin to the escape of blood may be determined by the tourniquet test of capillary fragility. The application of a tourniquet blocking the venous return of one arm produces a fresh crop of petechial hemorrhages in the skin. This test is best carried out by applying a blood pressure cuff maintained between the systolic and diastolic pressures for eight minutes.

Types of Purpura

The diseases manifested by purpura can be divided into those where the defect appears to be principally in the vessel wall and the platelets are present in normal numbers (nonthrombocytopenic purpura) and those in which the bleeding is primarily due to an inadequate number of platelets (thrombocytopenic purpura)

Purpura associated with normal platelets may occur as a manifestation of acute infectious diseases as a reaction to drugs and other toxins or in scurvy where the vascular injury results from deficiency of vitamin C However the most common type seen in children is *Henoch Schoenlein purpura* which is also designated as *anaphylactoid purpura* because of the belief that it may result from sensitization of the small blood vessels

Thrombocytopenic purpura may be secondary to diseases of the bone marrow such as leukemia and aplastic anemia which destroy the megakaryocytes which produce platelets *Idiopathic thrombocytopenic purpura* is associated with normal numbers of megakaryocytes in the marrow and apparently results from destruction of the platelets Certain types of purpura due to drug allergy are also apparently due to excessive destruction of platelets In this group also is included the rare thrombotic thrombocytopenic purpura characterized by purpura and widespread infarcts believed to result from aggregates of platelets in the small vessels

Allergy has been suspected as a cause of diseases in both the thrombocytopenic and nonthrombocytopenic groups Certain cases of both types are apparently clearly attributable to drug allergy Autosensitization to platelets is believed to be the cause of many or most cases of idiopathic thrombocytopenic purpura It is particularly in anaphylactoid purpura that allergy to foods or an allergic reaction to infection is frequently suspected as a causative factor However actual proof of either type of causative agent is usually difficult to establish

ANAPHYLACTOID PURPURA

Anaphylactoid or Henoch Schoenlein purpura is a generalized disease of the small blood vessels manifested by urticarial and purpuric skin lesions gastrointestinal and renal symptoms and involvement of the joints The visceral and joint symptoms may at times predominate and overshadow the purpuric manifestations Blood platelets are not affected

Etiology

The use of the name anaphylactoid purpura carries an implication of an allergic mechanism which can actually be proved only occasionally

The condition is most common in children from 3 to 14 years of age and somewhat more common in boys than in girls An allergic factor in at least some cases is suggested by the findings of Clement and Diamond that there was a family history of allergy in 25 per cent of the cases and a personal history of allergy in 30 per cent

The onset of anaphylactoid purpura not infrequently follows a week or two after an upper respiratory infection It has been suggested that the infection may lead to bacterial sensitization or that it may initiate autosensitization to the endothelial tissues of the small vessels Clear proof of either of these mechanisms is not possible Support for the theory of autosensitization is offered by animal experiments in which lesions similar to those of the human disease have been produced by injecting heterologous sera containing antibodies for the endothelium of the small vessels

Food allergy has been established as a cause in certain cases by demonstrating the relief of symptoms when specific foods were avoided and recurrence when they were added to the diet Foods which have been implicated include milk eggs lamb pork wheat onions carrots and berries The number of cases in which foods have been proved to be a factor is not great and it appears doubtful that this is a common cause of this type of purpura

Inhalants have been suggested as a cause of purpura but proved cases do not seem to be recorded in the literature

Symptoms

The skin rash characteristically appears at first as urticarial or papular lesions which become purpuric The most common locations are the extremities and buttocks The areas about the joints are particularly involved The face and trunk are seldom affected

The gastrointestinal symptoms consist of abdominal pain vomiting and hemorrhage from the gastrointestinal tract The severity of abdominal symptoms may suggest an acute surgical condition such as appendicitis or intussusception The diagnosis may usually be made on the basis of previous or associated skin lesions joint manifestations and increased capillary fragility In cases where exploratory operations have been done extensive edema and hemorrhage into the walls of the gastrointestinal tract have been found

The joint manifestations are periarticular swelling redness and pain with effusion at times They tend to be less painful than those occurring in rheumatic fever and usually clear in several days Several joints may be involved the knees and ankles are most often affected

The kidneys are also affected hematuria is fairly common and nephritis with oliguria and nitrogen retention is not unusual

Examination of the blood shows no typical findings the platelets are not reduced

Diagnosis

The diagnosis of anaphylactoid purpura must be based on clinical observation as no suitable tests are available The character of the rash in the early stages is often helpful When the skin lesions are slight or absent differentiation may be difficult

The establishment of foods or drugs as causative factors depends upon observation of improvement of symptoms when they are eliminated and recur

rence when they are again given during a free interval Skin tests with causative foods have been found to be positive occasionally but are more often negative so that they can only be considered suggestive of foods to be eliminated from the diet A food diary may also be helpful in directing suspicion to certain foods but the actual diagnosis must be based on the effects observed when the food is withdrawn from the diet and subsequently added during a free interval

Evaluation of the factor of bacterial sensitization must also be based on careful clinical evaluation The onset after an acute infection naturally raises the suspicion The severity of the purpura bears no relation to the severity of the infection and it may develop either during the infection or during convalescence The presence of persistent foci of infection should also be considered and these corrected by suitable means Skin reactions to bacterial vaccines or toxins may be obtained in some cases but interpretation of their significance is open to question

There are no established methods for evaluating the factor of autosensitization

Treatment

Obviously any specific allergen which may be established as a cause is eliminated Any existing infection of the nose and throat should be treated with suitable antibiotics chosen if possible on the basis of cultures and sensitivity tests In the absence of a demonstrable cause the greatest symptomatic relief is apparently afforded by corticotropin and cortisone derivatives

Prognosis

The course of anaphylactoid purpura is uncertain In some cases spontaneous recovery takes place within a few days More often it lasts several weeks and occasionally may prove fatal either from hemorrhage or nephritis

IDIOPATHIC THROMBOCYTOPENIC PURPURA

While allergic methods of diagnosis and treatment are not important in the clinical management of idiopathic thrombocytopenic purpura brief mention of the immunologic mechanism responsible for a considerable proportion of cases is of interest The striking feature of this type of purpura is the decrease in the number of platelets in the circulating blood The megakaryocytes which are the sources of platelets are present in the bone marrow in normal or increased numbers This suggests that the platelets are being destroyed or sequestered from the blood stream

Harrington Moore and others have shown that the plasma of many patients with this disease contains a factor which causes an abrupt drop in the platelet count of the circulating blood when injected into normal volunteers In microscopic preparations the plasma of the patient may be shown to produce agglutination of the platelets of the patient or of normal individuals This platelet agglutinin is apparently an autoantibody unrelated to the known blood types

In certain cases of thrombocytopenic purpura of newborn infants the plasma of the apparently normal mother has been shown to contain an agglutinin for the platelets of the infant but not for her own platelets These isoantibodies quite analogous to the antibodies for the Rh factor of red cells are believed to result from a previous pregnancy or from transfusions and to pass through the placenta to the infant

PURPURA DUE TO DRUGS

Purpura of both the nonthrombocytopenic and the thrombocytopenic types may be produced by allergy to drugs The form associated with normal numbers of platelets is most often caused by arsenicals iodides and salicylates while thrombocytopenia may be induced by sulfonamides arsenicals quinine Mesantion Sedormid and others

The nonthrombocytopenic type is frequently associated with other rashes of drug allergy and presumably *results in some manner from sensitization and* damage of the endothelium of the small blood vessels of the skin

The thrombocytopenic purpura due to drugs which is discussed in more detail in Chapter 21 apparently results from combination of the drug as a hapten with the platelets and the formation of agglutinins rather similar to those described in idiopathic thrombocytopenic purpura but specific for the drug platelet complex rather than normal platelets In the absence of the drug there is no agglutination or destruction of platelets When the drug is taken its combination with the platelets causes them to be specifically agglutinated and destroyed in the same manner that normal platelets are destroyed in idiopathic thrombocytopenia

In contrast to the rarity of purpura due to food allergy purpura due to drugs is not uncommon In all cases of purpura in children regardless of the number of platelets inquiry should be made as to the recent administration of drugs particularly those mentioned above All drugs should be stopped if possible In the case of drugs rapidly eliminated from the body marked improvement may be expected within a few days if the purpura is due to the drug

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Chapter 21

DRUG ALLERGY

SPECIAL FEATURES OF DRUG ALLERGY

Allergic reactions to drugs are far less common in children than in adults but sufficiently frequent to warrant consideration of their important differences from reactions to other allergens. Certain manifestations of drug allergy—urticaria, anaphylactic shock and contact dermatitis—are similar to the common allergic diseases previously described. Many other manifestations of drug allergy, such as drug fever, dermatitis medicamentosa, hepatitis and blood dyscrasias, *are clinical pictures not known to result from sensitization to the* naturally encountered allergens. The diagnosis of drug allergy is more difficult since the skin tests which are valuable in other forms of allergy, except for patch tests in contact dermatitis, are not reliable as evidences of allergy to nonprotein drugs. It is also impossible as a rule to demonstrate the presence of skin sensitizing or other antibodies in the serum.

Recognition of reactions to drugs as allergic phenomena is made difficult by the toxic properties of drugs. Most of the other allergens causing reactions in children—pollens, inhalants and foods—are harmless to normal persons, so that any *reaction resulting from exposure to them is presumably allergic*. On the other hand, the value of drugs, with a few exceptions such as penicillin and other antibiotics, depends upon their properties of altering bodily physiology and excessive doses are almost always toxic. Different persons vary in their susceptibility to these effects so that the dose which is beneficial in one may be toxic in another. The distinction between such hypersusceptibility to the toxic effects of a drug and an allergic reaction is not always easy but is important since the acquisition of allergic *sensitization completely* changes a patient's tolerance

for the drug and gives rise to symptoms which do not result from doses of any size in the child who is not specifically sensitized

Since antibodies are rarely demonstrable in allergy to nonprotein drugs the classification of reactions depends chiefly on clinical criteria When the drug is first given no dose produces the symptoms of drug allergy the sensitization is acquired through exposure and develops after an incubation period at least as long as the usual time of antibody formation that is after a week or more Once sensitization is acquired the reaction to subsequent doses may be immediate and the reaction may be produced by doses much smaller than were well tolerated at first Furthermore the symptoms of the allergic reaction are unrelated to the usual pharmacologic or toxic actions of the drug

Except for biologic drugs containing protein most drugs are not antigenic in the true sense of inducing antibody formation if injected into experimental animals They are believed to induce allergy by acting as haptens and combining with body protein With the exception of a few chemically very active compounds such reaction with protein is not demonstrable outside the body its chemical nature is unknown in most cases and the actual hapten protein conjugates have not been isolated

URTICARIA AND ANGIOEDEMA

Among the commonest manifestations of drug allergy are urticaria and angioedema The drug most frequently causing urticaria in children is penicillin Aspirin is another common etiologic agent but almost any drug or biologic product may occasionally provoke the reaction These reactions may take the form of simple urticaria or angioedema identical with those due to foods on the other hand the cutaneous lesions may be a part of a general anaphylactic reaction or when caused by penicillin one manifestation of a syndrome resembling serum sickness[4]

In any case of urticaria of unknown cause if the child has been taking any drug or medicine even the simplest it should be discontinued As a rule urticaria due to a drug appears within one to twelve hours after the medication has been taken and subsides when the drug is eliminated from the body The principal exception to this rule is urticaria due to penicillin which may develop several days after the low dose and persist for days or weeks after the drug is no longer detectable in the blood

When urticaria is due to a protein drug such as insulin skin tests with the drug are usually positive In the case of nonprotein drugs the skin tests are rarely positive and are not of diagnostic value

Urticaria due to insulin presents a special problem since *avoidance is often* impossible and there is no acceptable substitute Ordinary insulin is made from both pork and beef pancreas but special pure beef and pure pork insulin are available from the manufacturers Some patients having urticaria from the routine preparation are allergic to only one of these components while others react to insulin from any source The child should be tested with the separate beef and pork insulins starting with intracutaneous tests with U40 insulin diluted 1 10 If the reaction is to only one species the other may be used for sub

sequent treatment If insulin of both species reacts desensitization may be advisable *Injections of crystalline insulin are given one to three times a day* starting with one unit and increasing gradually until a dose adequate to control the diabetes is reached Concurrent use of antihistamine drugs is helpful in the desensitization In many mild cases the usual doses may be continued without desensitization if antihistamine drugs are given Severe anaphylactic reaction to insulin is very rare therefore one need not hesitate to continue treatment while suppressing the allergic manifestations

REACTIONS RESEMBLING SERUM SICKNESS

One of the most characteristic allergic reactions to penicillin is a syndrome which has all the clinical features of serum sickness After an incubation period of a week or two urticaria angioedema and arthralgia develop and persist for a period of a few days to two weeks or more Fever usually mild is often *present for a few days at the onset*

While the clinical picture corresponds in all details to that of serum sickness the immunologic features of serum sickness are absent *Skin* tests with penicillin are usually negative during and after the reaction and antibodies are rarely demonstrable

While recovery from true serum sickness almost invariably leaves the patient anaphylactically sensitized to the serum this type of sensitization only rarely results from the similar reaction to penicillin Patients who have had these reactions to penicillin show an increased incidence of allergic reactions to subsequent injections of penicillin but the second reaction is more often similar to the first than to the immediate anaphylactic type

Treatment of the serum sickness type of reaction to penicillin is the same as that of ordinary serum sickness drugs of the cortisone group are the most effective therapeutic agents

ANAPHYLACTIC REACTIONS

*Typical anaphylactic shock may occasionally be caused by repeated injec*tions of biologic medications which contain protein such as toxoids or by penicillin The report of fatal reactions of two identical infant twins to combined toxoid and pertussis vaccine has been cited in Chapter 6 but it should be noted that such reactions are very rare in children Sensitization results from *one or more previous injections of the same medication which may or may not* be followed by less violent manifestations of allergy

The incidence of anaphylactic sensitization to penicillin is apparently greater *in patients with an atopic hereditary tendency* and greater in patients *who have* received a number of injections at intervals of weeks or months than in those given prolonged courses of treatment For these reasons the repeated use of penicillin by injection *for the treatment* of respiratory infections in patients with asthma carries the risk of such a reaction The danger is less in children than in adults but still real enough to make the use of oral antibiotics preferable in infective asthma

A considerable number of reports of anaphylactic reactions to penicillin (mostly in adults) indicate that the patients had definite allergic reactions the significance of which was not recognized after one or more injections preceding that which caused a severe or even fatal reaction When giving penicillin by injection one should always ask whether the child has had the drug previously and whether any type of reaction resulted It is well to include this question in the initial history of allergic children and to mark the records of those who have had suspicious reactions in the past in a conspicuous manner so that the history will not be forgotten later

Anaphylactic sensitization to protein biologic drugs is almost invariably accompanied by a positive reaction to an intracutaneous test with the medication This type of sensitization to penicillin also is often but not always accompanied by a positive skin test When there is a history suggestive of an allergic reaction to a previous injection of penicillin it is best to substitute a different antibiotic if possible If there are compelling reasons for trying penicillin again a skin test should be done before starting treatment A scratch test with aqueous penicillin 20 000 to 50 000 units per milliliter or if this is not available with undiluted procaine penicillin is advised If this test shows a two plus or stronger reaction one should assume that the child has a high degree of anaphylactic sensitization On the other hand a negative reaction to the skin test cannot be taken as proof that the child may not have an immediate reaction from injection of the therapeutic dose and gives no indication of the possibility of a delayed urticarial reaction

The symptoms and treatment of these reactions are the same as those of anaphylactic shock due to heterologous serum or other causative agents and have been described in Chapter 5

GENERAL ATOPIC REACTIONS

Also identical in symptoms and treatment but occurring after the first injection and more properly classed as a general atopic rather than anaphylactic reaction is the reaction resulting from injecting vaccine derived from egg yolk into a child with a naturally acquired atopic sensitization to egg Most of the virus and rickettsial vaccines including typhus spotted fever and influenza virus vaccines but not the *Salk* poliomyelitis vaccine are *prepared by this method* and contain enough egg yolk protein to produce severe or even fatal allergic reaction in the atopic child highly sensitive to egg Such children almost invariably show immediate urticarial reactions to skin tests with egg protein and usually give a history of violent symptoms after eating eggs Children who show slight or moderate reactions to skin tests with egg but are eating eggs frequently without obvious symptoms resulting will usually tolerate the vaccine if given cautiously in divided doses starting with one tenth or less of the full dose

DRUG FEVER

A common manifestation of drug allergy which has no counterpart in allergy to naturally encountered extrinsic allergens but is seen in serum sickness is fever

This is caused most commonly by the sulfonamides but also by para aminosalicylic acid iodides arsenicals and other medications Nirvanol formerly used in the treatment of Sydenham s chorea produced drug fever in essentially all patients

When caused by a drug given in a continuous course of treatment the fever occurs abruptly after an incubation period of 7 to 14 days from the first dose The fever is usually spiking as high as 104° to 105 F and continues as long as the drug is taken When the drug is stopped the fever subsides as soon as it is eliminated from the body a matter of one or two days with most drugs After the fever subsides the child remains sensitive and an immediate rise of temperature usually follows another dose If the drug causing the fever is given periodically the sensitizing dose may have been eliminated from the body before sensitization is established so that the first evidence of sensitization is a prompt reaction to the next dose This was well illustrated in Milian s syndrome of the ninth day frequently noted when weekly injections of arsenicals were the customary treatment of syphilis but is also seen with periodic injections of mercuhydrin or repeated short courses of sulfonamides

Drug fever is often but not invariably accompanied by other manifestations of drug allergy most often dermatitis medicamentosa The combination of fever and a rash which may be either morbilliform or scarlatiniform often causes confusion with the contagious exanthemas The leukocyte count varies from normal values to a marked polymorphonuclear leukocytosis eosinophils are rarely increased

Autopsies on patients (mostly adults) dying in the course of drug fever characteristically show scattered lesions of the small arteries including those of the myocardium with degeneration of the media and perivascular infiltration of wandering cells Foci of necrosis in the liver lungs spleen and other organs are also frequently noted These visceral lesions suggest the potentially serious nature of this type of sensitization Complete recovery takes place rapidly if the causative drug is stopped promptly but death occasionally results from failure to recognize the nature of the fever and from continuation of the drug

Skin tests are of no value in establishing the diagnosis It is established on the basis of the temporal relationship of fever to the administration of a drug known to produce the condition and the subsidence of the fever when the drug is discontinued If further use of the same drug is necessary a cautious trial of half the usual dose will usually prove the diagnosis by a prompt rise of temperature

DRUG RASHES

The most frequent manifestations of drug allergy are skin rashes In addition to urticaria previously discussed drugs may cause eruptions of a variety of morphologic types Some of these are virtually specific for a certain group of chemically related compounds like the acneiform rashes of iodides and bromides Others may be produced by a limited number of different groups of drugs such as erythema nodosa resulting from sulfonamides and thiouracil and the fixed drug eruptions produced by phenolphthalein barbiturates and sulfonamides

The two most important types dermatitis medicamentosa due to systemic administration of drugs and contact dermatitis due to their topical application may be caused by a wide variety of medications The former may be due to sulfonamides barbiturates para aminosalicylic acid arsenicals antibiotics or other drugs the latter to local anesthetics sulfonamides penicillin mercury compounds antihistamines and other medications applied to the skin surface

The appearance of these rashes does not depend on the drug used but varies in different stages of the condition The initial eruption due to a systemically administered drug is usually a diffuse maculopapular rash which appears after an incubation period of one or two weeks involves chiefly the trunk and arms and fades promptly when the drug is stopped If the use of the drug is continued the rash may assume a purpuric or a confluent scarlatiniform appearance and may go on to exfoliation At this stage the clearing of the rash after stopping the medication is less rapid During a second course of treatment the rash may appear without the usual incubation period These rashes are often accompanied by drug fever

Contact dermatitis caused by topical medications is usually an erythemato vesicular eruption limited to the area of contact and not accompanied by systemic symptoms It does not differ materially from contact dermatitis due to nonmedicinal allergens (Chapter 18)

These two morphologically different rashes represent the results of different types of exposure on the same basic sensitization Children who have had severe contact dermatitis due to the topical use of one of the sulfonamide drugs are apt to react to subsequent oral administration of the same drug with generalized dermatitis medicamentosa and children with severe rashes due to systemic drugs may show a positive patch test if the drug is readily absorbed through the skin surface

Since the patch test involves the same type of exposure as the production of contact dermatitis it is a fairly reliable method of proving the etiologic diagnosis of this type of rash Because of the uncertainty of absorption from the skin surface and the question of what constitutes a comparable exposure of the sensitized cells of the skin it cannot be considered a reliable method of diagnosing rashes resulting from systemic medication Since scratch and intra cutaneous tests are of no value the latter diagnosis is susceptible of proof only by the clinical course during avoidance and subsequent reexposure

In most cases of drug dermatitis discontinuation of exposure produces prompt relief If other treatment is necessary the drugs of the cortisone groups are most effective and can be used in otherwise healthy children without hesitation since the condition is self limited and a week or two of therapy is usually ample

HEPATITIS

When hepatitis results from the use of drugs differentiation of toxic and allergic effects is not easy In the case of such well known hepatotoxic agents as tetrachloroethylene and carbon tetrachloride the liver damage is apparently

a direct toxic effect On the other hand hepatitis caused by sulfonamides arsenicals and Atabrine is often accompanied by fever skin rashes and other signs of drug allergy and shows the previously described features of an acquired sensitization the previous tolerance for the drug decreasing sharply when sensitization is acquired The course of hepatitis due to drug allergy is usually benign if its nature is recognized and further use of the drug avoided However occasional cases may progress to fatal liver atrophy

BLOOD DYSCRASIAS

Among the most serious reactions to drugs are blood dyscrasias Any or all of the formed elements of the blood may be depressed or destroyed by various drugs As in hepatitis the distinction between toxic and allergic reactions cannot be sharply defined Aplastic anemia in which red cells leukocytes and platelets are all decreased may be caused by arsenicals sulfonamides chloramphenicol and hydantoin derivatives The course of this illness with an incubation period often lasting weeks or months and with symptoms persisting and often progressing for months after the last exposure suggests a toxic effect rather than an allergic sensitization Death occurs in a large proportion of cases despite discontinuation of the drug as soon as the condition is recognized

Agranulocytosis without significant changes in the red count or platelets is classically linked with amidopyrine a drug now rarely administered to children in America It may also be caused by the related drug Butazolidin and also by sulfonamides Tridione Mesantoin arsenicals and thiouracil Agranulocytosis due to amidopyrine strikingly illustrates the features of an acquired sensitization but the picture in cases due to the other drugs mentioned is less typical The condition usually develops after the drug has been used for weeks or months often there is a gradual decline of the granulocyte count rather than the abrupt onset typical of an allergic drug reaction The course is usually acute but chronic forms also occur Without treatment mortality from secondary infection is approximately 80 to 90 per cent but with adequate antibiotic treatment a considerable proportion of cases may be saved When recovery takes place subsequent use of the same drug usually causes a prompt recurrence

Thrombocytopenic purpura may be caused by arsenicals sulfonamides quinine quinidine Mesantoin and Sedormid the latter a sedative used more in England than America In cases due to Sedormid Ackroyd has shown that addition of the drug to the patient s blood in vitro after recovery causes agglutination and lysis of platelets This reaction occurs with the serum of the patient and his own or normal platelets It is believed that the drug combines with the platelets to produce an antigenic compound which reacts with an antibody in the patient s serum A similar reaction has also been demonstrated in thrombocytopenic purpura due to quinine and may probably apply to the other drugs causing the disease As practical tests for clinical use Ackroyd suggests the inhibition of clot retraction (a manifestation of lack of platelets) of the patient s blood when the drug is added and also the production of local

purpura by a patch test with the drug Both of these tests must be done after recovery from the active stage of the disease

Thrombocytopenic purpura due to drugs that are rapidly excreted from the body is usually of brief duration That due to arsenic may be persistent During the active stage the risk of severe or fatal hemorrhages is considerable Treatment with cortisone derivatives offers the most effective relief After recovery strict avoidance of the causative drug is essential

Purpura with a normal number of platelets apparently due to capillary damage may also be caused by certain drugs such as iodides salicylates and arsenicals This condition resembles in general the nonthrombocytopenic purpura due to foods (Chapter 22)

SPECIFICITY AND DURATION OF DRUG ALLERGY

The specificity of drug allergy is of practical interest in case it is necessary to consider the subsequent use of a drug chemically related to that which has caused an allergic reaction Unfortunately it varies so greatly in different cases that no general rule is possible One child reacting to a drug of the sulfonamide group may tolerate others without reaction while another will react to the entire group The group specificity is usually broadest in the case of contact dermatitis Children with contact sensitization to one of the synthetic local anesthetics or to one of the sulfonamides may be expected to react to all drugs of the respective groups

The duration of sensitization after a reaction is of practical importance also In general it must be assumed to persist indefinitely The chief exceptions are in cases of urticarial reactions to penicillin This type of sensitization sometimes disappears in the course of a few weeks or months but the variable course and the possibility of severe anaphylactic reactions make unsafe the assumption that a child has lost his sensitization

DESENSITIZATION

The possibility of desensitizing children allergic to insulin by injections of gradually increasing doses of crystalline insulin has been mentioned A similar procedure may also be effective in allergy to other protein containing biologic drugs Attempts at desensitization with nonprotein drugs have shown less favorable results While the procedure is occasionally successful it may also cause alarming reactions in some cases When an acceptable substitute for the drug causing the reaction is available its use is to be preferred to desensitization

SUPPRESSION OF DRUG ALLERGY BY OTHER MEDICATIONS

Many of the symptoms of drug allergy are suppressed by adequate doses of cortisone and its derivatives and the simple urticarial reactions are often suppressed by antihistamine drugs This naturally suggests the possibility of continuing the causative drug and controlling the allergic symptoms with one of these medications The advisability of such a course of action must be judged in the individual case on the basis of several factors (1) the danger of the

disease for which the allergenic drug is being used (2) the availability of a suitable substitute (3) the severity of the drug allergy (4) the knowledge of the risk of more severe allergic reactions due to the same allergenic drug and (5) the risk of side effects from cortisone derivatives In cases of urticaria due to insulin the drug is usually essential there is no acceptable substitute (except in cases specifically sensitive to beef or pork insulin) the risk of more severe allergic reactions is negligible and if antihistamine drugs will control the urticaria their use is warranted Similar reasoning may be justified when urticaria results from penicillin being given for bacterial endocarditis However in the case of drugs which are known to cause the more serious types of clinical sensitization and visceral lesions such as the sulfonamides continuation of the drug in face of an allergic reaction is dangerous Whenever another drug will produce the desired effect it should be substituted

The routine administration of antihistamine drugs with injections of penicillin has also been suggested as a method of avoiding reactions This is not recommended The majority of reactions to penicillin are of the delayed type and occur long after the effects of a single dose of an antihistamine are over It is possible that this procedure may suppress mild immediate allergic reactions but this is not desirable since mild immediate reactions are often the only warning of the possibility of a severe anaphylactic reaction to a subsequent injection If the child is developing a progressively severe anaphylactic sensitization one must anticipate a reaction which may be far too severe to be controlled by the routine dose of the antihistamine It is much safer to realize the trend of events and avoid further injections

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Chapter 22

PHYSICAL ALLERGY

During the third quarter of the nineteenth century Bourdon and also Blachez reported cases of urticaria due to cold During the following fifty years other instances of the same phenomenon were described Duke in a series of publications between 1925 and 1935 reported many additional cases of cold urticaria and added apparent allergic reactions to light heat mechanical stimulation and effort He proposed the general term *physical allergy* to denote the entire group of phenomena which morphologically and physiologically resembled the usual allergic diseases but were induced by physical agents rather than antigenic materials He classified the manifestations of physical allergy as *contact reactions* in which the physiologic effects occurred in the tissue directly exposed to the physical agent and *reflex reactions* in which the shock organ was remote from the actual point of exposure

The concept of allergy to physical agents conflicted with the increasingly *accepted view of allergy as an antigen antibody reaction since there was no* evidence that a specific material antigen was involved However subsequent experience has left no doubt that cold urticaria and dermatographia or urticaria due to mechanical stimulation are relatively common The extensive studies of Lewis on the blood vessels of the skin gave strong evidence that such reactions involve the release of histamine or some physiologically similar H substance but did not touch on any antibody mechanism In certain cases of urticaria due to cold and light the serum of the patient has been found to passively sensitize the skin of normal persons to the same stimulus suggesting that in these instances an antibody may be involved but giving no direct evidence as to the nature of the antigen In many other highly sensitive cases of urticaria due to cold and light and in most other types of physical allergy attempts at passive transfer of sensitization by the serum have failed

Since the writings of Duke the term physical allergy has become firmly established and there is no doubt that typical urticarial wheals may be produced in certain patients by cold trauma and less often by heat and light However most modern authorities have been more conservative than Duke in making the diagnosis of physical allergy regardless of whether or not they consider evidence of an antibody mechanism essential for the use of the word allergy

As has been pointed out in Chapter 3 the symptoms of allergic diseases which are basically caused by sensitization to material allergens or infection may be profoundly influenced by nonspecific factors which include physical agents such as cold heat light and mechanical irritation A large proportion of patients with asthma or allergic rhinitis regardless of the basic cause are made worse or their latent symptoms activated by breathing cold air In many cases chilling of the body surface suffices to precipitate an attack Some patients with rhinitis sneeze when exposed to bright sunlight Patients with eczema or urticaria are almost invariably made worse by heat and mechanical irritations such as scratching Both respiratory and skin allergies may be aggravated by effort asthma as a result of increased respiratory effort eczema and urticaria through increase of the skin temperature and sweating These allergic diseases are primarily due to material allergens and exacerbations in the same patient may be caused by different secondary factors at different times The reaction to physical agents varies with the activity of the basic allergy and may disappear completely when it is well controlled In the management of such cases the recognition and avoidance of the physical factors are important but they are not properly classed as examples of true physical allergy and making such a diagnosis often leads to neglect of the search for the underlying material allergens

With this more critical classification of physical allergy the reflex type described by Duke is rarely if ever diagnosed and effort is generally omitted from the list of causative factors The clear cut cases are urticarial reactions at the site of exposure to cold heat light or mechanical stimulation Cases of urticaria proved to be primarily due to light and heat are relatively uncommon in all age groups particularly in children The principal manifestations of physical allergy in the pediatric age groups are *cold urticaria* and urticaria due to mechanical stimuli denoted as *dermatographia* or *urticaria factitia*

Even when the term is thus restricted it is impossible to establish a similar mechanism in all reactions of the group In most cases there are direct or indirect grounds to suggest that the release of histamine is involved but the evidence of an antigen antibody mechanism is variable While the sera of some patients with urticaria due to cold or light readily induce passive sensitization of normal skin those of others who are apparently equally sensitive are completely inactive In urticaria due to heat and in dermatographia attempts at passive transfer of sensitization generally give negative results and the few reports of success are inconclusive Grouping these various conditions together as physical allergy does not imply a similar immunologic mechanism in all in fact there is reason to question whether all cases of cold urticaria involve the same basic mechanism

COLD URTICARIA

Urticarial reactions induced by contact with cold are not infrequent in children and offer a clear cut example of physical allergy This condition affects both patients with other atopic diseases and those without apparent evidence of such a hereditary tendency There is little evidence that cold is a significant secondary factor in urticaria due to other causes and most cases react specifically to this stimulus

The characteristic reaction is the appearance of an urticarial wheal sharply localized to the area of exposure This may be induced by cold air especially when wind increases the chilling by immersion in cold water or by contact with ice When the hands or face are affected the reaction may be manifested by diffuse swelling redness and tingling without clearly defined wheals The reaction may occur during the period of exposure or within a few minutes after the tissues return to normal temperature In many cases the ingestion of iced drinks or ice cream is followed by swelling of the lips and mouth abdominal cramps or diarrhea indicating that the mucosae are also affected Patients with severe sensitivity may suffer syncope and collapse with marked hypotension after generalized chilling particularly immersion in cold water

The studies of Horton and associates indicate that the reaction is produced by liberation of histamine in the exposed tissues If one extremity of a sensitive patient is chilled in a water bath the systemic effects of histamine are manifested by fall in blood pressure and increased excretion of free hydrochloric acid in the stomach Occlusion of the venous and lymphatic return from the chilled extremity by a tourniquet prevents the systemic reaction indicating that it depends upon a substance transmitted through the circulation rather than a reflex through the nerves The general collapse reaction resulting from general chilling in severe cases is also consistent with the effect of circulating histamine

In numerous cases of cold urticaria the serum of the patient has been shown to produce local passive sensitization in normal human skin so that the sensitized site reacts to exposure to cold In other cases which are apparently equally sensitive attempts at passive transfer have given negative results The demonstration of passive sensitization strongly suggests that an antigen antibody mechanism is involved in the reaction The failure to produce transfer in other cases may idicate a different type of mechanism or simply that an antibody is present in the tissues but not in the circulating plasma

If an antigen antibody mechanism is involved the nature of the antigen is unknown At least in those cases where the serum produces passive transfer the antigen is presumably present in normal skin as well as that of the patient Attempts to extract from frozen normal skin an antigen producing the reaction have failed It appears more probable that the antibody involved reacts in the cold but not at normal body temperature with an isoantigen normally present in the tissues Other antibodies reacting only in the cold with antigens of the normal blood cells have been described Well known examples are the cold hemolysins of syphilitic paroxysmal hemoglobinuria and the cold agglutinins induced by virus pneumonia Although some patients with paroxysmal hemo-

globinuria show urticarial reactions in the skin when exposed to cold the average patient with cold urticaria shows no evidence of syphilis and his serum does not contain hemolysins or cold agglutinins Another abnormal plasma protein which is affected by cold is cryoglobulin sometimes detected in the serum of patients with blood dyscrasias and manifested by the occurrence of purpuric rashes on chilling of the skin Some patients with cryoglobulinemia show cold urticaria but most attempts to demonstrate cryoglobulin in the serum of patients with uncomplicated cold urticaria have failed

The diagnosis of cold urticaria is usually apparent from the history It may be confirmed by reproducing the typical lesion with the application of an ice cube to the surface of the forearm Depending on the degree of sensitivity contact for 10 seconds to 10 minutes may be required When the ice is removed no reaction is apparent but as the skin resumes normal temperature a wheal develops within 10 minutes and is sharply limited to the area of contact

In the treatment of cold urticaria the most important measure is avoidance of chilling by suitable clothing and limitation of activities during cold weather It is essential that swimming in cold water be avoided because of the danger of a general reaction It has been suggested that many cases in which good swimmers have drowned in cold water may be due to such general reactions to cold allergy Patients with cold urticaria must be extremely careful in entering any water for swimming as it is impossible to state a definite temperature which will be safe

Antihistamine drugs are helpful in many cases They may be used prophylactically to lessen reactivity by administration shortly before unavoidable exposure to cold air and therapeutically to hasten the subsidence of lesions which have already developed

Many authors have recommended programs of daily cool baths with progressive decrease of the water temperature and duration of the bath Since the severity of the reaction may change spontaneously over a period of time it is difficult to judge the efficacy of such hardening procedures Another procedure that has been widely advocated but whose value is hard to prove is the injection of graduated doses of histamine in an attempt to lessen the body s reaction to it This same form of treatment has been used in many types of allergic diseases but clear evidence that the reaction to histamine can be thus decreased is still lacking

HEAT URTICARIA

Definite instances of urticaria specifically caused by heat are rare particularly in children Since heat both general and local is well known as a nonspecific aggravating factor in urticaria due to other basic causes the diagnosis of heat allergy should not be made without careful consideration of other etiologic agents Evidence of an antibody mechanism is doubtful Avoidance of exposure and use of antihistamine drugs are logical measures for control which may be helpful whether the effect of heat is specific or contributory

ALLERGY TO LIGHT

Exposure to light has many effects on the skin of normal children and those affected by various diseases The most obvious effect is sunburn It is well known that children vary greatly in susceptibility to sunburn depending on the texture and pigmentation of the skin and on toughening through previous exposure Such differences have no relation to allergy in the strict sense Exposure to light may also have an adverse effect on children affected by such diseases as porphyria hydroa aestivale and lupus erythematosus These effects are not to be confused with true allergy to light which is rare in adults and practically unknown in children It is manifested by urticaria localized at the site of exposure of the skin to light Some patients are affected by visible light and others by ultraviolet rays but the effect in each case is specifically caused by one portion of the spectrum Treatment consists of care in avoiding excessive exposure the use of lotions which filter the rays of the sun and cautious toughening of the skin by repeated brief exposures

URTICARIA DUE TO MECHANICAL IRRITATION

*Dermatographia (urticaria factitia) or urticarial lesions produced by rub*bing or scratching the skin is a common condition in both adults and children This is generally considered to be a manifestation of physical allergy but whether it is produced by an immunologic mechanism is doubtful Passive transfer of the reaction to normal skin by the serum of the patient has been reported in a few cases but numerous other attempts have failed Lewis and *his associates considered dermatographia an exaggeration of the redness and* slight swelling produced in normal skin by scratching

The lesion consists of an elongated urticarial wheal with the characteristic flat top and sharply raised margin surrounded by an area of erythema The reaction is readily produced by gently scratching the skin with a relatively blunt object such as a wooden applicator The wheal is limited to the length of the scratch but its width which may be 5 to 10 mm exceeds the actual area of contact

Since this type of lesion is readily produced at will the diagnosis of dermatographia is easy However it should be borne in mind that in most patients who are suffering from active urticaria due to any cause elongated wheals may be elicited by scratching the skin Therefore apparent dermatographia has no significance in the presence of general urticaria The diagnosis is made only when the condition persists in the absence of spontaneously occurring hives

Dermatographia is not a serious condition and treatment is rarely necessary The reactions may be inhibited by antihistamine drugs when they are troublesome or unsightly

Marked dermatographia may be troublesome when allergy skin tests are done particularly by the scratch technique In such cases all tests show one plus or two plus reactions and differentiation of *significant reactions is impos*sible When all tests appear to give positive reactions a control test with saline or diluting fluid is essential If this shows a moderate degree of reaction the

results of the tests must be evaluated with care and only the marked reactions obviously larger than the control considered indicative of sensitivity This difficulty can be avoided by testing by the method of passive transfer

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Chapter 23

ALLERGY IN RELATION TO COLLAGEN DISEASES

A considerable volume of medical literature has been devoted to the group of diseases classed as collagen diseases and the relation of allergy to their development Collagen is the intercellular substance of connective tissue and as such is present in all organs of the body Focal degeneration of collagen fibers has long been known as a histologic feature of rheumatic fever and rheumatoid arthritis Klinge noted the occurrence of similar changes in other diseases of the mesenchymal tissues and also in experimental sensitization of animals The concept and classification of collagen diseases is largely an outgrowth of his studies which he interpreted as evidence that collagen degeneration was a manifestation of allergy For this reason the classification of collagen diseases and the belief that they are related to allergy have been historically associated

The diseases generally included in the group are rheumatic fever rheumatoid arthritis periarteritis nodosa lupus erythematosus scleroderma and dermatomyositis All of these diseases show similar degenerative lesions of the collagen in some this change is most marked in the walls of the small blood vessels and granulomatous collections of histiocytes and endothelial cells are frequently associated

The histologic lesions appear to be inflammatory but do not contain bacteria nor have viruses been isolated The etiology of all of these diseases is uncertain and the classification of them together does not rest on any clear evidence of an etiologic relationship between them In fact local collagen degeneration is present in experimental disease produced by other mechanisms than allergy An etiologic relationship is however suggested by the observation

that certain patients have illnesses which combine typical features of two or more of the diseases of the group permitting only a classification as undifferential collagen disease All of the diseases of the group respond more or less favorably to cortisone and its derivatives This is consistent with an etiologic relationship but in view of the wide variety of other diseases benefited is hardly conclusive evidence

In two of these conditions rheumatic fever and periarteritis considerable evidence has been accumulated suggesting the importance of allergy as a pathogenic factor The evidence of the importance of sensitization in the other diseases of the group is far less impressive Until further supporting facts are established attempts to class all collagen diseases as allergic are premature Klemperer and other distinguished pathologists have cautioned against the inference of an immunologic mechanism of sensitization from purely histologic evidence

The following brief discussions are intended to cover only the relationship of these diseases to allergy For details of diagnosis and treatment one should refer to general pediatric texts

RHEUMATIC FEVER

Rheumatic fever is one of the common diseases of childhood manifested chiefly by fever polyarthritis and carditis and less often by chorea subcutaneous nodules epistaxis and erythematosus or purpuric skin rashes Pathologic changes are most marked in the heart which shows inflammatory and proliferative changes in the valves myocardium and pericardium The basic lesion is the Aschoff body a microscopic focus of collagen degeneration adjacent to a small vessel which becomes infiltrated with mononuclear and endothelial cells While this is seen in its most typical form in the myocardium variants are found in the endocardium pericardium aorta and subcutaneous tissues The subcutaneous nodules which may exceed 1 cm in diameter are considered aggregates of the characteristic histologic lesion Bacteria are not present in the lesions

Etiologic Factors

It is now generally agreed that acute attacks of rheumatic fever follow infections by the Group A beta hemolytic streptococcus most often pharyngitis or tonsillitis Recovery from the acute infection (Phase I) is followed by a latent period of one to three weeks (Phase II) during which the child is apparently well and then the onset of acute rheumatic fever (Phase III) At this stage the streptococci are often no longer present in the throat If they are still present antibiotics have no effect on the evolution of the rheumatic process However when streptococcus infections are prevented by prolonged administration of sulfonamides or penicillin there are no recurrences of rheumatic fever

In epidemics of infection by Group A hemolytic streptococci only a fraction of children infected by the organism develop rheumatic fever but essentially all who have had previous attacks of rheumatic fever develop exacerbations

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Additional evidence from human pathology is offered by the resemblance of the pathologic lesions noted in fatal serum sickness to those of rheumatic fever Lesions suggestive of the Aschoff body have also been demonstrated in the myocardium of patients dying during reactions to sulfonamide drugs

Thus the predominance of evidence from a variety of sources supports the view that rheumatic fever is a manifestation of allergy to the Group A hemolytic streptococcus The relationship to streptococcus infection is of great practical value in prevention of recurrences and the demonstration of the streptococcus in throat cultures and of antistreptolysin O in the serum are helpful aids in diagnosis However the concept that this relationship depends on an allergic reaction is so far only of theoretical interest

RHEUMATOID ARTHRITIS

In many respects rheumatoid arthritis closely resembles rheumatic fever and at the onset differentiation between the two may present a difficult problem It is primarily a disease of early adult life the childhood form is not common It tends to run a chronic course with persistent and often deforming arthritis affecting first the joints of the hands and feet Subcutaneous nodules are similar to those of rheumatic fever but cardiac lesions are rare

Histologic features are focal proliferation of mononuclear cells and collagen degeneration with granuloma formation

There is no specific relationship to hemolytic streptococcus infection and the rule of infection in general is not clearly established although focal infection is often suscepted as an etiologic factor

The serum of most patients with rheumatoid arthritis shows the property of agglutinating hemolytic streptococci While this reaction is fairly characteristic and paradoxically is not present in acute rheumatic fever where the importance of the streptococcus is proved it does not appear to be a truly specific antibody reaction as other bacteria and sheep cells sensitized with amboceptor are also agglutinated by the same sera The sedimentation rate is generally increased and C reactive protein is present in the serum during the active stages

Rich has considered the pathologic lesions similar to those of sensitization phenomena but supporting evidence from other sources is scanty and no specific antigen has been suggested as a cause

PERIARTERITIS NODOSA

Periarteritis nodosa is a progressive and usually fatal disease characterized by vascular lesions peripheral neuritis nephritis and skin rashes usually purpuric It may occur at any age but is not common in children The typical pathologic lesion is a necrosis of segments of the media of small arteries with perivascular infiltration and formation of small aneurysms

In adults periarteritis has been noted to occur rather frequently in patients who have suffered for some years from chronic asthma most often of the infective type When periarteritis occurs in an asthmatic patient there is a characteristically high eosinophil count usually 20 to 30 per cent Patients

with periarteritis which does not follow asthma show a neutrophilic leukocytosis and rarely eosinophils The relation of periarteritis to asthma suggests that both may result from sensitization but coexistence of the two diseases is not common in children

Lesions similar to those of periarteritis are seen at autopsy in patients dying with serum sickness or severe febrile reactions to sulfonamides iodides and other drugs Rich has shown that identical lesions are produced in rabbits by injecting large doses of horse serum The vascular lesions occur at the time of antibody formation and of serum sickness

From the histologic standpoint there is no doubt the lesions are identical Clinically the differences between serum sickness drug fever and periarteritis nodosa are very striking Serum sickness and drug fever are usually mild illnesses tending to spontaneous recovery in a few days while spontaneous periarteritis nodosa is a chronic progressive and usually fatal disease This difference might naturally be due to failure to recognize and eliminate the allergen in the spontaneously developed disease In no case of periarteritis *occurring spontaneously without exposure to drugs has a specific antigen been* determined In cases following infective asthma (in adults) treatment by attempting to eliminate foci of infection has not affected the progressive course of the periarteritis

These clinical differences naturally raise the question whether all diseases showing the histologic lesion of periarteritis are similar in etiology Some authors have suggested the general term *polyarteritis* to apply to all with spontaneous periarteritis nodosa and arteritis due to drugs in separate subordinate classifications

From the practical standpoint allergic methods of diagnosis and treatment have not proved to be of value in the management of cases of periarteritis nodosa arising spontaneously in children who have not been taking drugs If the child has been taking sulfonamides thiouracil iodides or other allergenic drugs the effects of eliminating them should obviously be observed before arriving at the diagnosis of periarteritis nodosa The allergic hypothesis is of interest chiefly as a basis for further investigation of this obscure disease Meanwhile *cortisone offers the most effective therapy*

DISSEMINATED LUPUS ERYTHEMATOSUS

One of the most typical collagen diseases with extensive and widespread degeneration of collagen is disseminated lupus erythematosus The lesions involve particularly *the blood vessels serous membranes and synovia Clinically* the condition is characterized by a prolonged and intermittent course usually terminating fatally It is not related to lupus vulgaris and the butterfly type of lesion on the face which gives the disease its name is not consistently present It is primarily a disease of young women but may affect children

The most typical diagnostic feature is the presence in the bone marrow and peripheral blood of the L E cell of Hargraves This is a polymorphonuclear leukocyte containing large masses of chromatin stained deeply by Wright s stain

These cells can be found in most cases of the disease by repeated smears and are highly specific although they have also been found in patients with drug reactions to Apresoline The nature of this phenomenon is not established There is evidence that it is produced after the blood is drawn by protein factors present in the plasma

No significant evidence has been offered to prove the importance of allergy in this condition There seems to be an unusual incidence of drug allergy in patients affected by the condition but no relationship to the atopic diseases Since the skin lesions are made worse by light physical allergy has been proposed as an etiologic factor The progression of the disease in the dark and the occurrence of extensive visceral lesions without skin changes make this theory untenable

SCLERODERMA AND DERMATOMYOSITIS

Both scleroderma and dermatomyositis are rare chronic diseases of the skin and connective tissues with involvement of the skeletal muscles in the latter They show the degenerative lesions of collagenous tissue which is typical of the group The etiology in both cases is unknown and there is no substantial evidence to relate either disease to allergy

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Chapter 24

GENERAL PEDIATRIC CARE OF THE ALLERGIC CHILD

CHARACTERISTICS OF THE ALLERGIC CHILD

Early in the study of allergic diseases the erroneous impression was developed that the allergic especially the atopic child was usually of well to-do parents superior in intelligence and education sensitive emotionally as well as physically and neurotic Even a characteristic physical type with light hair and complexion blue eyes and freckles was described It is now apparent that the allergic child does not consistently differ in any of these respects from other children All economic strata and all races and types are equally affected by allergic diseases The allergic children show the same range of intelligence as other children and are equally advanced in school studies unless chronic illness has handicapped them Their emotional reactions are those of healthy children or of children who have suffered in equal degree of disability from other chronic illnesses Aside from their specific sensitizations and their inborn tendency to develop new allergies they are exactly like other children

GENERAL PRINCIPLES

As indicated in the discussions of the various diseases it is quite essential that the allergic child avoid the allergens to which he is definitely known to be sensitive It is also prudent as a preventive measure to avoid or minimize exposure to substances particularly inhaled dusts to which he is not sensitive but which are known to be active allergens There is also justification for applying similar preventive measures to the care of the preallergic child,

who because of the presence of atopic disease in his parents brothers or sisters is suspected of having inherited the tendency but who has not yet shown symptoms However an excessive number of restrictions based more on general principles than clear reasons tends to foster undue worry of the parents and invalidism of the child

The basic consideration in the care of the allergic child should be that as few restrictions be placed on his way of life as possible without undue risks This of course requires good clinical judgment rather than a long list of arbitrary restrictions No blueprint can be given as to how far limitation of *diet of activity in the form of exercise or sports or other restrictions in the usual* way of life of the patient should be advocated Restrictions are necessitated by symptoms not by diagnoses The prime consideration in the management of the allergic child is to make him as much like his other nonallergic playmates compatible with his problem and his capacities

DIET

The problem of the introduction of foods into the diet of the so called preallergic child has received careful attention by Glaser He has advocated the use of a soybean formula to replace one with cow s milk and has given statistical evidence to show that this modifies the incidence of major allergic manifestations in a group of children so treated when compared to a control group Not only are they spared a milk sensitivity but the incidence of other sensitizations is also apparently reduced This is an interesting and important contribution It is not the type of study which can be readily duplicated but will take many years of careful observation to be substantiated by other workers Meanwhile most infants will receive cow s milk unless they develop definite allergic symptoms Certainly there can be no question that such highly allergic foods as egg fish and wheat should be introduced into the child s diet only after other more readily tolerated foods have been used It is also unwise to use any mixed foods in the diet of an allergic infant It is best to begin with foods which have been proved on empirical grounds to be relatively low in producing allergies There is no longer the great tendency there was years ago to have the infant eating all foods by the time he has reached the age of 4 or 5 months In a child suspected or proved to be allergic it is much wiser to introduce a single food at a time and observe for any clinical evidence of sensitization Since on the whole meats are well tolerated and are only rarely associated with allergic symptoms these may be introduced quite early into the infant s dietary regimen Since they are a good source of protein there is little need for the early introduction of egg If for specific reasons milk is eliminated from the diet other forms of protein either soybean preparations or others are entirely effective *in maintaining nutrition and growth in this age* group If milk is eliminated from the diet it is well to administer calcium supplements (Neo Calglucon calcium lactate tablets etc)

There is no question that some of these allergic infants may be exquisitely sensitive to egg and fish In some rare cases mere contact with these foods

without ingestion may produce severe angioedema or even asthma In the allergic child the introduction of egg may well be delayed without harm until (1) the child is completely asymptomatic or (2) sufficiently mature so that no untoward reactions are anticipated that is at the end of the first year When egg is added to the diet it is well to try a boiled egg using only a small fraction of the yolk If this is well tolerated larger amounts of yolk may be tried over the succeeding days and finally some of the albumin may also be administered In some patients quantitative factors may be important A child may tolerate egg occasionally yet should he receive egg more often clinical symptoms may be produced In the early neonatal period many fleeting skin eruptions have been associated with the introduction of orange juice into the diet Often allergy to this food is suspected but again actual proof is infrequent Since in this period the prime effort is to get the baby off to a good start it is often well to administer synthetic ascorbic acid rather than orange juice as such

Nuts are highly allergenic and may produce profound allergic reactions in the sensitive individual Although peanuts are members of the legume family and not actually biologically related to the other forms of nuts they too may produce severe reactions It is good pediatric practice not to allow nuts to be given to the small child The aspiration of this material may produce serious consequences and the best form of treatment lies in prevention Often it is simpler for the allergic child s parents simply not to have nuts in the home rather than to tell the child he may not have them

It is of some interest that long acting Adrenalin is commonly distributed in a vehicle of peanut oil Reactions to this material however appear to be quite rare A long acting form of epinephrine is now available which does not contain this oil *

Children s food dislikes need not necessarily indicate a special allergic sensitization However it should be remembered that as adults our food tastes are largely based on considerations other than their nutritional value Many children will refuse eggs as such yet will tolerate them in other foods in which their taste and flavor is masked For example they may like French toast and yet refuse egg in other forms Within reason therefore it seems unwise to force foods which the child dislikes If eating is made a pleasurable experience *without the proverbial it s good for you or he will eat it for* me only if I feed him then the number of feeding problems seen by the pediatrician *will* be significantly reduced

It is often impossible to administer foods to which a patient is highly allergic without producing immediate prompt and often violent vomiting This series of events is not unusual in the child who is highly sensitive to egg and who despite his objections is inveigled to take an egg usually in the form of eggnog or a similar concoction Despite this prompt attempt to rid the body of this highly active allergen enough may occasionally be absorbed so that severe angioedema and urticaria asthma or even vasomotor collapse may follow this procedure

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Sus Phrin (see Chapter 4)

When a basic diet has been worked out in a patient who is doing well new foods should be introduced at regular intervals perhaps four to six days in order to enrich his diet and place as few limitations as possible on the child s eating habits As was noted in Chapter 9 the permanent elimination of foods from a child s diet based solely on results of reactions obtained to skin tests is unsound and poor medicine It should not become necessary for the child to steal foods in order to satisfy his appetite or his cravings The consulting physician must come to a definite conclusion regarding the importance of a specific item of food in the patient s diet as it relates to the patient s symptoms If there is convincing evidence that there is a casual relationship between symptoms and the ingestion of a food then it should be removed from the diet However in the older child it is well to point out to him this causal relationship and it is not unusual for full cooperation to be obtained from even a fairly young patient

DIET OF MOTHER DURING PREGNANCY

Whether it is possible to modify the newborn s sensitivities as a result of dietary restriction in the mother during pregnancy is a concept which is of more than academic importance Unfortunately statistics are difficult to obtain It has been suggested that the diet of the pregnant mother be limited with respect to the major food allergens which are noted in the infantile period namely milk and egg Since these foods are not essential no harm would be derived from this dietary restriction if other sources of protein and calcium are substituted However at this date it is not possible to give objective data on this problem

FURNISHINGS

Some general statements can be made with regard to the furnishings and care of the child s room Since a good part of the time is spent in this room proper attention should be paid to its furnishings The room should be kept as dust free as possible This implies that all dust producers be minimized Cotton throw rugs which can be laundered at regular intervals seem to be entirely satisfactory With the allergic child substitution of a foam rubber or Dacron pillow for his feather pillow may give considerable relief It is important however that if the allergic child shares his room with another sibling that the feather pillow also be removed from the nonallergic sibling because of the intimate contact which exists

The mattress may either be covered with a plastic cover or be made of latex or other relatively nonallergenic material Wool blankets should be completely enclosed in cotton covers after they have been laundered

With respect to fuzzy woolly toys it is often well to eliminate these until one has an opportunity to check whether or not their presence in anyway modifies the child s allergic symptoms At present all types of synthetic relatively nonallergenic materials are used in the manufacture of toys and it is well to check their composition and content before their purchase

the mortality rate high there is no sound medical reason why this unnecessary complication should be allowed to occur

Immunization with other biologicals such as pertussis vaccine and diphtheria and tetanus toxoid is on the whole well tolerated by this group of children Where possible these should be administered at about the same time that they would be given to nonallergic individuals Since local and febrile reactions are not uncommon in normal nonallergic children the occurrence of such reactions in the allergic group should not be too distressing to the physician If these reactions are beyond those expected it is often advisable to separate these biologicals and administer them individually perhaps in smaller doses Since anaphylactic reactions to heterologous sera such as tetanus antitoxin of horse origin are much more prone to occur in the group of allergic children than in the general population it is important to maintain their active immunity by repeated and periodic stimulating doses of toxoid It is good medical practice to have the parent or older child carry with him a card stating that we are dealing with an allergic patient who has been actively immunized to diphtheria and tetanus It is also well to give the date of the last booster dose and indicate that antitoxin need not be administered for casual and minor trauma

Allergic children should also receive poliomyelitis vaccine To date millions of doses of poliomyelitis vaccine have been administered The incidence of allergic complications both in the normal and the allergic group of patients has been practically nil Salk vaccine contains a small amount of penicillin but is tolerated by most children who have previous reactions to therapeutic doses of this antibiotic In the case of children who have had serious anaphylactic reactions to penicillin the same type of skin tests and precautions advised for the use of antisera (Chapter 6) may be employed

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APPENDIX

MEASURES FOR THE CONTROL OF HOUSE DUST

House dust is one of the most important causative factors of allergic disease Complete avoidance is not practical but careful measures to lessen exposure are an important part of the treatment of the child who is allergic to this substance In cases of mild dust allergy such measures may suffice to control the symptoms but in the more sensitive cases injection treatment to lessen susceptibility is also usually necessary

The extent of the precautions justified will depend on the degree of allergy and other circumstances If the family is contemplating a change of residence the choice of the house may greatly aid in carrying out an effective program Usually it is necessary to work with the existing residence The greatest effort is concentrated in the room where the child sleeps but attention to the living room is also required

In general relatively new houses of modern design with simple interior construction are easier to keep free of dust than old remodeled buildings with elaborate cornices and valances Old floors with cracks between the boards exposed pipes and elaborate radiators present problems Radiant heating is ideal but water or steam is acceptable if the radiators are accessible for thorough cleaning Hot air heat is the least satisfactory as dust tends to be disseminated through the ducts and filtering systems are rarely adequate

Since the average child spends the greater portion of his time out of the house or in his bedroom the latter is the most important room to be considered For the initial cleaning the room and its closets should be completely emptied The entire room should then be scrubbed—woodwork floor radiators and painted walls with water and soap or detergent and papered walls with a suitable cleaner The floor should be wooden or covered with linoleum cracks and openings around pipes should be sealed as completely as possible If there is a hot air vent in the room it should be covered with several layers of cheesecloth and sealed at the edges with tape

When the cleaning has been completed a minimum of essential furniture which has also been scrubbed should be returned to the room This should

consist only of a steel or wooden bed chairs dresser and mirror Upholstered furniture and large rugs should not be used One or two small washable rugs are permissible Curtains should be simple and easily washable

Bedding should consist of Dacron or foam rubber pillows a foam rubber mattress or a good cotton mattress covered with a dustproof cover cotton sheets cotton or wool blankets and a simple washable cotton spread Quilts and comforters are to be avoided A thin cotton mattress pad is permissible if washed weekly

Only essential clothing should be placed in the dresser and closet that which is not in use at the time should be stored elsewhere Toys of metal wood or plastic may be allowed in the room and only two or three books or magazines at one time Fuzzy animal toys excess books bookcases plants souvenirs and knickknacks that catch dust are not permitted in the bedroom The room should be essentially as bare and simply furnished as a hospital room

The amount of change to be made in the rest of the house will depend on the severity of the child s dust allergy the success of injection treatment the age and habits of the child and the expense permissible When possible provision of a rather barely furnished room with a wooden or linoleum floor and without rugs or upholstered furniture for play and television will lessen the need for consideration of drastically altering the parlor or living room

In general no changes in the living room are necessary until the effects of cleaning up the bedroom and injection treatment have been observed for a period of several weeks When parlor furnishings are to be changed foam rubber is preferable to other upholstery materials Washable cotton slip covers over upholstered furniture and relatively simple and preferably washable draperies are desirable Rug pads and wall to wall carpeting are best avoided

In so far as possible the dust sensitive child should be kept out of attics cellars and storerooms and should not be in rooms where cleaning is in process

Maintenance of the dust free bedroom requires daily care The entire room should be dusted with a moist oily or specially prepared dust cloth daily at first and at least twice a week after the desired results have been accomplished The floor should be mopped at the same time with a damp or oily mop The door to the bedroom and its closets should be kept closed when not in use the windows closed as much as possible and heat turned on only when necessary The remainder of the house should be thoroughly cleaned with a vacuum cleaner once a week and carefully dusted twice a week

Oily emulsions for lessening the liberation of dust from rugs draperies and upholstered furniture are available * These demonstrably lessen the amount of dust formation and when properly applied do not affect the appearance of most fabrics The process of application which is rather laborious is done by cleaning establishments in many cities These measures are to be considered for the living rooms and not for the bedroom of the allergic child which should be so barely furnished that such a procedure is unnecessary

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They are useful adjuncts in the protection of the child allergic to dust but do not take the place of injection treatment.

Electrical devices are available for removing dust from the air of rooms, the most efficient being those with electrostatic precipitators rather than mechanical filters. These effectively remove dust from the air which is circulated through them and can keep the air of a small closed room relatively free of dust but are rarely needed if other precautions are taken. Window air conditioners which recirculate the air of the room through mechanical filters are of some value in the control of indoor dust. Their greatest value in the control of allergic disease is in preventing the entrance of pollens from outside.

LISTS OF ALLERGEN EXTRACTS FOR TESTING

The following lists are prepared for the guidance of the physician in ordering an initial supply of allergens for skin testing. Since the number of potential allergens is large, a reasonable number will depend on the extent to which he intends to devote his practice to the allergic diseases. For this reason each list is divided into two parts: first, the most essential allergens; and second, supplementary allergens which will probably be needed if many cases are handled. The supplementary lists may be enlarged according to location and type of practice.

The strengths of extracts ordinarily used for intracutaneous tests are given in protein nitrogen units per milliliter except in the case of those allergens not ordinarily standardized in this way. The lowest dilution given is safe for the initial tests on most children.

Inhalants

Essential Inhalants	*Protein Nitrogen Units per Milliliter*		
Cat epithelium	10	100	1,000
Dog epithelium	10	100	1 000
Horse epithelium	10	100	1,000
Rabbit epithelium	10	100	1,000
Sheep wool			1 000
Feathers		100	1 000
Kapok	10	100	1 000
Cottonseed	10	100	1 000
Flaxseed	10	100	1 000
Silk			1 000
Pyrethrum			1 000
House dust	1:10	concentrated	(not standardized)
Karaya gum	1%	(weight/volume)	
Supplementary Inhalants			
Cow epithelium	10	100	1 000
Goat epithelium		100	1 000
Mouse epithelium	10	100	1,000
Rat epithelium	10	100	1 000
Parakeet feathers		100	1 000
Canary feathers		100	1,000
Orris root	10	100	1,000
Tobacco			1 000
Ca to be 1 0 1 1			
Gum (arabic)	1%	(weight/volume)	
Gum tragacanth	1	(weight/volume)	

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Molds

	Protein Nitrogen Units per Milliliter			
Essential Molds				
Alternaria		100	1,000	
Hormodendrum		100	1,000	
Supplementary Molds				
Aspergillus		100	1,000	
Candida		100	1,000	
Cephalothecium		100	1,000	
Dematium		100	1,000	
Helminthosporium		100	1,000	
Mucor		100	1,000	
Penicillium		100	1,000	

Foods

Essential Foods				
Cow's milk				10,000
Cow's casein				10,000
Cow's whey				10,000
Goat's milk				10,000
Goat's whey				10,000
Egg white		100	1,000	
Egg yolk		100	1,000	
Corn			1,000	
Rice			1,000	
Wheat			1,000	
Beef			1,000	
Chicken			1,000	
Lamb			1,000	
Pork			1,000	
Chocolate			1,000	
Apple			1,000	
Banana			1,000	
Orange			1,000	
Pineapple			1,000	
Prune			1,000	
Carrot			1,000	
Green pea			1,000	
Onion			1,000	
Spinach			1,000	
Tomato			1,000	
White potato			1,000	
Peanut		100	1,000	
Mustard	10	100		
Flounder			1,000	
Halibut			1,000	
Tuna			1,000	
Supplementary Foods				
Barley			1,000	
Oats			1,000	
Rye			1,000	
Duck			1,000	
Turkey			1,000	
Coffee			1,000	
Tea			1,000	
Cantaloupe			1,000	
Cherry			1,000	
Grape			1,000	
Grapefruit			1,000	
Black pepper			1,000	
Cod			1,000	
Salmon			1,000	
Scallop			1,000	
Lemon			1,000	
Peach			1,000	

Supplementary Foods	*Protein Nitrogen Units per Milliliter*	
Strawberry		1 000
Asparagus		1 000
Cabbage		1 000
Lettuce		1 000
Lima bean		1 000
Mushroom		1 000
Squash		1 000
String bean		1,000
Sweet potato		1 000
Almond	100	
Pecan	100	
Clam		1 000
Oyster		1 000
Shrimp		1 000

Miscellaneous

Essential Miscellaneous Allergen Extracts				
Horse serum	1 100	1 10		
Tuberculin	1 100 000		1 10 000	1 1 000
Supplementary Miscellaneous Allergen Extracts				
Honeybee	1	10	100	1 000
Yellow jacket	1	10	100	1 000
Wasp	1	10	100	1 000

Pollens

The pollen extracts must be selected according to location Those li ted in Chapter 8 for various sections of the United States may be considered the essentials for the respective areas Supplementary items may be selected by reference to Wodehouse *The Hay Fever Plants* Durham s chapter in Vaughan and Black *Practice of Allergy* and Samter and Durham *Regional Allergy* or by local study and inquiry

Other Methods of Standardizations

Many of the large manufacturers of allergen extracts do not employ the protein nitrogen basis of standardization * The impossibility of accurately converting other types of standardization into protein nitrogen units has been explained in Chapter 8 For *most pollens* 1 000 protein nitrogen units per milliliter equals *roughly* 0 02 mg of total nitrogen per milliliter 2 000 total nitrogen units 2 000 Noon pollen units or 1 500 extract (weight of pollen/volume of fluid) This approximation is sufficiently accurate for use in choosing suitable strengths of extracts for intracutaneous testing but *not* for changing extracts in the course of injection treatment In testing with foods protein nitrogen and total nitrogen may be considered essentially equivalent In other cases the advice of the manufacturer should be followed

Group Antigens

In order to lessen the number of skin tests to be done on a child it is common practice to test with mixtures of several of the most important allergens

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in a biologic group, for example, a mixture of several tree pollens important in the area. If the mixture gives no reaction, the group is eliminated, but if the mixture reacts, its components are subsequently tested separately. This method may be advantageously used in testing with fish and shellfish and as a screening test for tree pollens in patients whose symptoms are not predominantly in the tree pollen season. In most other groups the use of group tests is apt to defeat its own purpose by increasing the total number of tests. The use of group antigens for treatment is not recommended except in the case of the grass pollens.

Dilution of Extracts

If a considerable volume of allergy is handled, it is desirable and economical to purchase relatively concentrated extracts and make dilutions in the office. If extracts preserved with glycerin are used, they must be diluted at least 1:10 for intracutaneous testing to avoid irritative reactions.

Buffered saline (Evans) with 0.4 per cent phenol is a suitable diluting fluid. It consists of:

Sodium chloride	5	Gm
Monobasic potassium phosphate (KH_2PO_4)	0.36	Gm
Dibasic sodium phosphate ($Na_2HPO_4 \cdot 12H_2O$)	1.43	Gm
Phenol	4	Gm
Distilled water	1,000	ml

This solution is sterilized by autoclaving.

Since the most common dilution is tenfold, it is convenient to prepare and keep on hand a considerable number of sterile vials containing either 9 ml or 4.5 ml of diluting fluid. With careful sterile technique the diluting fluid is accurately pipetted into sterile vials and each sealed with a sterile rubber cap. When a 1:10 dilution is desired, 1 ml of extract is withdrawn with a sterile syringe and needle and squirted into a vial containing 9 ml of diluting fluid without removing the cap of either vial. If vials containing 4.5 ml of diluting fluid are used, 0.5 ml is injected.

PREPARATION OF DUST EXTRACT

The great majority of children allergic to house dust may be adequately tested and treated with stock extract of house dust allergen, preferably prepared from dust collected in homes in the same general part of the country where the patient lives. However, in occasional cases the preparation of an extract of dust from the patient's own home for testing and treatment is desirable. This is the case in which the history is strongly suggestive of dust sensitization but the skin reaction to the stock extract is equivocal, or in which the symptoms are related to a particular house and cannot be explained on the basis of pets or other known factors. The procedure can be readily carried out in the office laboratory with relatively simple equipment.

For the collection of an adequate sample of dust a vacuum cleaner is practically essential. Dust should not be collected shortly after the use of

insecticides in the house Dusts from houses where there are dogs or cats are of little significance unless the skin tests to these animals are slight or negative The parent is instructed to bring in enough packed dust from the vacuum cleaner bag to fill a one pound candy box The bulk of this consists of accumulated sweepings from all parts of the house but just before the dust is collected the child's bedroom should be cleaned and the bedding and any upholstered furniture swept with suitable attachments

The dust is placed in a wide mouthed jar for defatting Ether petroleum ether and carbon tetrachloride are suitable solvents for this purpose All of these must be handled with care the first two because they are highly flammable the last because of the toxicity of its vapor The dust is covered with a slightly larger volume of solvent shaken vigorously and the dirty solvent poured off When this procedure has been carried out with three fresh portions of solvent the dust is placed on filter paper allowed to drain thoroughly and spread out to dry in a well ventilated room

When the solvent has completely evaporated the dust is placed in a jar covered with just enough buffered saline extracting fluid to thoroughly saturate it and placed in the refrigerator for twenty four to forty eight hours The extract is then filtered off through coarse filter paper the amount obtained being increased by pressing the wet dust with a spatula If the amount of dust is scanty the extract may be squeezed out by rolling it in cloth and twisting firmly

The crude extract is placed in Visking cellophane tubing (24/32 inch in diameter is suitable) which is tied securely above and below The extract is dialyzed against running tap water for twenty four hours then against buffered saline for two hours to restore its ionic content The extract is then filtered with suction through a Seitz filter into sterile vials

Sterility is tested by adding 0 4 ml to 10 ml of thioglycollate medium and incubating for four days It is essential that the culture medium used be one which permits the growth of anaerobic as well as aerobic organisms

No standardization is necessary but the special dust extract is carefully compared with stock dust in simultaneous intracutaneous tests on the patient The tests are made with a 1 10 dilution of each followed if necessary by the undiluted material No advantage is to be expected from the use of the extract of the patient's own dust if it gives a smaller skin reaction than the stock extract If the special dust gives a distinctly larger reaction it should be used for treatment When both extracts give identical reactions it is reasonable to treat the patient with a mixture of equal parts of the autogenous and stock extracts

Only those with special training should attempt the preparation of extracts of other allergens than house dust

STERILIZATION BY FILTRATION

Allergen extracts and sera for passive transfer are inactivated by heat and therefore are sterilized by passage through a bacterial filter The *Seitz filter* is best adapted for this use The physician who plans to prepare sera for passive

transfer and extracts of dust from his patients houses should be equipped with one and be familiar with its use This filter consists of a metal cup in two parts which screw together and a special disposable asbestos filter pad The outlet of the filter is passed through the stopper of a suction flask preferably so arranged that the filtrate passes directly into a sterile vial placed inside the flask

The filter pad absorbs a small amount of the material passed through it slightly reducing both the volume and potency of the fluid recovered Since the amount of loss is dependent on the size of the filter pad it is well to use the smallest size of filter convenient for the volume of fluid to be handled The 25 ml size is the most useful in the office For filtering very small amounts (2 to 8 ml) of fluid a miniature Seitz filter the Swinny filter * which fits onto a Luer Lok syringe is available The fluid is forced through the filter by pressure on the plunger of the syringe rather than suction

The Seitz filter is sterilized with the filter pad in place and with the two metal parts firmly screwed together When the filter pad has been wet with the fluid to be filtered the metal parts are again screwed tighter to avoid leakage around the pad Suction is applied to the flask by a water suction pump If the filtrate is caught in a sterile vial placed inside the flask it is carefully removed with sterile forceps and closed with a sterile cap If the filtrate is in the body of the flask it must be transferred to a sterile vial with careful aseptic technique

Sterility Tests

After the extract or serum has been bottled and capped a sample is withdrawn with a sterile syringe for a sterility test This should be done with a culture medium in which both aerobic and anaerobic organisms will grow Thioglycollate medium is recommended The culture medium should be at least 8 cm deep in the tube about 15 ml suffices The sample inoculated is 0 3 ml which should be well mixed into the culture medium The culture is incubated four days at 37 C and then examined in a strong light The development of cloudiness in the medium indicates contamination identifying the organism is unnecessary Contaminated extract may be again passed through the Seitz filter and the sterility test repeated

* Supplied by Becton Dickinson and Co

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